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**(54) Title:** NODULISPORIC ACID DERIVATIVES**(57) Abstract**

The present invention relates to novel nodulisporic acid derivatives, which are acaricidal, antiparasitic, insecticidal and anthelmintic agents.

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**TITLE OF THE INVENTION**  
**NODULISPORIC ACID DERIVATIVES**

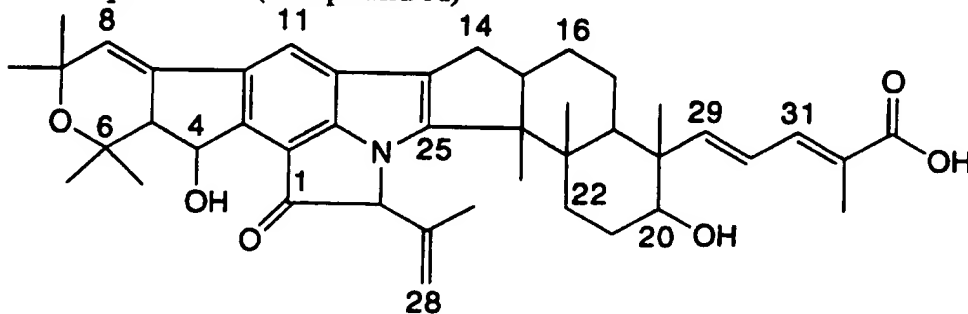
**CROSS REFERENCE**

- 5           This is a continuation-in part of co-pending application U.S.S.N. 08/406,619, filed March 20, 1995, which is hereby incorporated by reference.

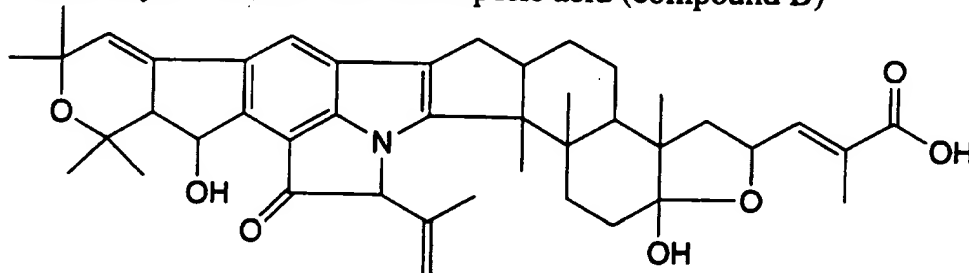
**BACKGROUND OF THE INVENTION**

- 10           Nodulisporic acid and two related components are antiparasitic agents and ectoparasiticial agents isolated from the fermentation culture of *Nodulisporium* sp. MF-5954 (ATCC 74245). These three compounds have the following structures:

- 15   nodulisporic acid (compound A)



- 20   29,30-dihydro-20,30-oxa-nodulisporic acid (compound B)



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- (4) optionally substituted C<sub>2</sub>-C<sub>10</sub> alkynyl,  
 (5) optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
 (6) optionally substituted C<sub>5</sub>-C<sub>8</sub> cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl,  
 cycloalkyl and cycloalkenyl are 1 to 3 groups independently  
 selected from  
 (i) C<sub>1</sub>-C<sub>5</sub> alkyl,  
 (ii) X-C<sub>1</sub>-C<sub>10</sub> alkyl, where X is O or S(O)<sub>m</sub>.  
 (iii) C<sub>3</sub>-C<sub>8</sub> cycloalkyl,  
 (iv) hydroxy,  
 (v) halogen,  
 (vi) cyano,  
 (vii) carboxy,  
 (viii) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are  
 independently H or C<sub>1</sub>-C<sub>10</sub> alkyl,  
 (ix) C<sub>1</sub>-C<sub>10</sub> alkanoylamino, and  
 (x) aroyl amino wherein said aroyl is  
 optionally substituted with 1 to 3 groups independently  
 selected from R<sup>f</sup>  
 (7) aryl C<sub>0</sub>-C<sub>5</sub> alkyl wherein said aryl is optionally  
 substituted with 1 to 3 groups independently selected from  
 R<sup>f</sup>,  
 (8) C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl  
 (9) a 5- or 6-membered heterocycle containing from 1  
 to 4 heteroatoms independently selected from oxygen, sulfur  
 and nitrogen atoms optionally substituted by 1 to 3 groups  
 independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>10</sub> alkyl  
 and halogen, and which may be saturated or partly  
 unsaturated,  
 R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are independently OR<sup>a</sup>, OCO<sub>2</sub>R<sup>b</sup>, OC(O)NR<sup>c</sup>R<sup>d</sup>; or  
 R<sub>1</sub>+R<sub>2</sub> represent =O, =NOR<sup>a</sup> or =N-NR<sup>c</sup>R<sup>d</sup>;  
 R<sub>5</sub> and R<sub>6</sub> are H; or  
 R<sub>5</sub> and R<sub>6</sub> together represent -O-;  
 R<sub>7</sub> is (1) CHO, or

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- (13) optionally substituted C3-C8 cycloalkyl  
 (14) optionally substituted C5-C8 cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl, cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl are from 1 to 10 groups independently selected from hydroxy, C1-C6 alkoxy, C3-C7 cycloalkyl, aryl C1-C3 alkoxy, NR<sup>g</sup>R<sup>h</sup>, CO<sub>2</sub>R<sup>b</sup>, CONR<sup>c</sup>R<sup>d</sup> and halogen,  
 5 (15) C1-C5 perfluoroalkyl,  
 10 (16) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from C1-C5 alkyl, C1-C5 perfluoroalkyl, nitro, halogen and cyano,  
 (17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen  
 15 optionally substituted by 1 to 4 groups independently selected from C1-C5 alkyl, C1-C5 alkenyl, C1-C5 perfluoroalkyl, amino, C(O)NR<sup>c</sup>R<sup>d</sup>, cyano, CO<sub>2</sub>R<sup>b</sup> and halogen, and which may be saturated or partly unsaturated;  
 R<sup>b</sup> is  
 20 (1) H,  
 (2) optionally substituted aryl,  
 (3) optionally substituted C1-C10 alkyl,  
 (4) optionally substituted C3-C10 alkenyl,  
 (5) optionally substituted C3-C10 alkynyl,  
 25 (6) optionally substituted C3-C15 cycloalkyl,  
 (7) optionally substituted C5-C10 cycloalkenyl, or  
 (8) optionally substituted 5- to 10-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;  
 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
 30 independently selected from  
 (i) hydroxy,  
 (ii) C1-C6 alkyl,  
 (iii) oxo,

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to 3 groups independently selected from  $R^g$ , hydroxy, thioxo and oxo;

$R^e$  is

5

- (1) halogen,
- (2)  $C_1$ - $C_7$  alkyl,
- (3)  $C_1$ - $C_3$  perfluoroalkyl,
- (4)  $-S(O)_mR^i$ ,
- (5) cyano,
- (6) nitro,
- (7)  $R^iO(CH_2)_v-$ ,
- (8)  $R^iCO_2(CH_2)_v-$ ,
- (9)  $R^iOCO(CH_2)_v$ ,

10

(10) optionally substituted aryl where the substituents are from 1 to 3 of halogen,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, or hydroxy,

15

- (11)  $SO_2NR^gR^h$ , or
- (12) amino;

$R^f$  is

20

- (1)  $C_1$ - $C_4$  alkyl,
- (2)  $X$ - $C_1$ - $C_4$  alkyl, where  $X$  is O or  $S(O)_m$ ,
- (3)  $C_2$ - $C_4$  alkenyl,
- (4)  $C_2$ - $C_4$  alkynyl,
- (5)  $C_1$ - $C_3$ -perfluoroalkyl,
- (6)  $NY^1Y^2$ , where  $Y^1$  and  $Y^2$  are independently H or  $C_1$ - $C_5$  alkyl,
- (7) hydroxy,
- (8) halogen, and
- (9)  $C_1$ - $C_5$  alkanoyl amino,

25

$R^g$  and  $R^h$  are independently

30

- (1) hydrogen,
- (2)  $C_1$ - $C_6$  alkyl optionally substituted with hydroxy, amino, or  $CO_2R^i$
- (3) aryl optionally substituted with halogen, 1,2-methylenedioxy,  $C_1$ - $C_7$  alkoxy,  $C_1$ - $C_7$  alkyl or  $C_1$ - $C_3$  perfluoroalkyl,

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(6) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl,  
 cycloalkyl and cycloalkenyl are 1 to 3 groups independently  
 selected from

- 5 (i) C<sub>1</sub>-C<sub>3</sub> alkyl,  
 (ii) X-C<sub>1</sub>-C<sub>6</sub> alkyl, where X is O or S(O)<sub>m</sub>,  
 (iii) C<sub>5</sub>-C<sub>6</sub> cycloalkyl,  
 (iv) hydroxy,  
 (v) halogen,  
 10 (vi) cyano,  
 (vii) carboxy, and  
 (viii) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are  
 independently H or C<sub>1</sub>-C<sub>6</sub> alkyl,

(7) aryl C<sub>0</sub>-C<sub>3</sub> alkyl wherein said aryl is optionally  
 15 substituted with 1 to 3 groups independently selected from  
 R<sup>f</sup>,

(8) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,

(9) a 5- or 6-membered heterocycle containing from 1  
 20 to 4 heteroatoms independently selected from oxygen, sulfur  
 and nitrogen atoms optionally substituted by 1 to 3 groups  
 independently selected from hydroxy, oxo, C<sub>1</sub>-C<sub>6</sub> alkyl and  
 halogen, and which may be saturated or partly unsaturated,

R<sub>8</sub> is

- (1) H,  
 (2) OH, or  
 25 (3) NH<sub>2</sub>;

R<sub>9</sub> is

- (1) H or  
 (2) OH;

R<sub>10</sub> is

- (1) C(O)OR<sup>b</sup>,  
 (2) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,  
 30 (3) C(O)NR<sup>c</sup>R<sup>d</sup>,  
 (4) NHC(O)OR<sup>b</sup>,  
 (5) NHC(O)NR<sup>c</sup>R<sup>d</sup>,  
 (6) CH<sub>2</sub>OR<sup>a</sup>,  
 (7) CH<sub>2</sub>OCO<sub>2</sub>R<sup>b</sup>,

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- 5 (2) optionally substituted aryl,  
(3) optionally substituted C<sub>1</sub>-C<sub>7</sub> alkyl,  
(4) optionally substituted C<sub>3</sub>-C<sub>7</sub> alkenyl,  
(5) optionally substituted C<sub>3</sub>-C<sub>7</sub> alkynyl,  
(6) optionally substituted C<sub>5</sub>-C<sub>7</sub> cycloalkyl,  
(7) optionally substituted C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, or  
(8) optionally substituted 5- to 10-membered  
heterocycle containing from 1 to 4 heteroatoms  
independently selected from oxygen, sulfur and nitrogen;  
10 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
independently selected from  
(i) hydroxy,  
(ii) C<sub>1</sub>-C<sub>3</sub> alkyl,  
15 (iii) oxo,  
(iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,  
(v) aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
(vi) hydroxy C<sub>1</sub>-C<sub>3</sub> alkyl,  
(vii) C<sub>1</sub>-C<sub>7</sub> alkoxy,  
20 (viii) hydroxy C<sub>1</sub>-C<sub>3</sub> alkoxy,  
(ix) amino C<sub>1</sub>-C<sub>3</sub> alkoxy,  
(x) cyano,  
(xi) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
(xii) C<sub>1</sub>-C<sub>3</sub> alkyl-S(O)<sub>m</sub>,  
25 (xiii) C<sub>5</sub>-C<sub>6</sub> cycloalkyl optionally substituted  
with 1 to 4 groups independently selected from R<sup>e</sup>,  
(xiv) C<sub>5</sub>-C<sub>6</sub> cycloalkenyl,  
(xv) halogen,  
(xvi) C<sub>1</sub>-C<sub>3</sub> alkanoyloxy,  
30 (xvii) C(O)NR<sup>g</sup>R<sup>h</sup>,  
(xviii) CO<sub>2</sub>R<sup>i</sup>,  
(xix) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
wherein the aryl substituents are 1,2-methylenedioxy or 1 to  
5 groups independently selected from R<sup>e</sup>,

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- (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- 5 (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;
- (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
- (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,
- (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,
- (9) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
- 10 (10) aminocarbonyl,
- (11) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl
- (12) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or
- R<sup>g</sup> and R<sup>h</sup> together with the N to which they are attached form a 5- to 6-
- 15 membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;
- R<sup>i</sup> is
- (1) hydrogen,
- (2) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (3) C<sub>1</sub>-C<sub>4</sub> alkyl,
- 20 (4) optionally substituted aryl C<sub>0</sub>-C<sub>4</sub> alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, and hydroxy;
- all other variables are as defined under Formula I.

25

In another preferred embodiment, the present invention provides compounds of Formula I wherein

- R<sub>1</sub> is
- (1) hydrogen,
- (2) optionally substituted C<sub>1</sub>-C<sub>3</sub> alkyl,
- 30 (3) optionally substituted C<sub>2</sub>-C<sub>3</sub> alkenyl,
- (4) optionally substituted C<sub>2</sub>-C<sub>3</sub> alkynyl,
- where the substituents on the alkyl, alkenyl, and alkynyl are 1 to 3 groups independently selected from
- (i) methyl,



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from hydroxy, C<sub>1</sub>-C<sub>2</sub> alkoxy, aryl C<sub>1</sub>-C<sub>3</sub> alkoxy, NR<sup>g</sup>R<sup>h</sup>, CO<sub>2</sub>R<sup>b</sup>, CONR<sup>c</sup>R<sup>d</sup> and halogen,

(10) trifluoromethyl,

5

(11) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from methyl, trifluoromethyl and halogen,

10

(12) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from methyl, trifluoromethyl, C(O)NR<sup>c</sup>R<sup>d</sup>, CO<sub>2</sub>R<sup>b</sup> and halogen, and which may be saturated or partly unsaturated;

R<sup>b</sup> is

15

(1) H,

(2) optionally substituted aryl,

(3) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,

(4) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenyl,

(5) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynyl,

(6) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl,

(7) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, or

20

(8) optionally substituted 5- to 6-membered heterocycle containing from 1 to 4 heteroatoms

independently selected from oxygen, sulfur and nitrogen;

where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups

25

independently selected from

(i) hydroxy,

(ii) C<sub>1</sub>-C<sub>3</sub> alkyl,

(iii) oxo,

(iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,

30

(v) aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,

(vi) hydroxy C<sub>1</sub>-C<sub>4</sub> alkyl,

(vii) C<sub>1</sub>-C<sub>4</sub> alkoxy,

(viii) hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxy,

(ix) amino C<sub>1</sub>-C<sub>4</sub> alkoxy,

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- 5  $R^f$  is (11) amino;  
 (1) methyl,  
 (2) X-C<sub>1</sub>-C<sub>2</sub> alkyl, where X is O or S(O)<sub>m</sub>,  
 (3) trifluoromethyl,  
 (4) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently H or methyl,  
 (5) hydroxy,  
 (6) halogen, and  
 (7) acetylamino,
- 10  $R^g$  and  $R^h$  are independently  
 (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>  
 (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;  
 (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,  
 (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,  
 (9) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 (10) aminocarbonyl,  
 (11) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl  
 (12) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or
- 25  $R^g$  and  $R^h$  together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;
- 30  $R^i$  is (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,  
 (3) C<sub>1</sub>-C<sub>4</sub> alkyl,  
 (4) optionally substituted aryl C<sub>0</sub>-C<sub>6</sub> alkyl, where the aryl substituents are from 1 to 3 groups independently

"Alkyl" as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-  
5 butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles,  
10 as well as benzofused carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include  
15 mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

20 The term "heterocycle", unless otherwise specified, means mono- or bicyclic compounds that are saturated or partly unsaturated, as well as benzo- or heteroaromatic ring fused saturated heterocycles or partly unsaturated heterocycles, and containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen. Examples of  
25 saturated heterocycles include morpholine, thiomorpholine, piperidine, piperazine, tetrahydropyran, tetrahydrofuran, dioxane, tetrahydrothiophene, oxazolidine, pyrrolidine; examples of partly unsaturated heterocycles include dihydropyran, dihydropyridazine, dihydrofuran, dihydrooxazole, dihydropyrazole, dihydropyridine,  
30 dihydropyridazine and the like. Examples of benzo- or heteroaromatic ring fused heterocycle include 2,3-dihydrobenzofuranyl, benzopyranyl, tetrahydroquinoline, tetrahydroisoquinoline, benzomorpholinyl, 1,4-benzodioxanyl, 2,3-dihydrofuro(2,3-b)pyridyl and the like.

ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

Compounds of the present invention are named based on the trivial name of the parent compound, nodulisporic acid (compound A), and their position numbers are those as indicated in formula I.

Compounds of the present invention are prepared from the three nodulisporic acids (Compounds A, B and C), which in turn are obtained from the fermentation culture of *Nodulisporium* sp. MF-5954 (ATCC 74245). The description of the producing microorganism, the fermentation process, and the isolation and purification of the three nodulisporic acids are disclosed in US Patent 5,399,582, issued March 21, 1995, which is hereby incorporated by reference in its entirety.

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in a protic solvent such as methanol, ethanol, water, tetrahydrofuran/water or dimethylformamide/water and the like at from 0°C to the reflux temperature of the solution. Alternatively, the resultant esters may be hydrolyzed by treatment with a Lewis acid, such as

5 magnesium chloride, aluminum chloride, titanium tetra-isopropoxide and the like in a protic solvent such as methanol, ethanol, isopropanol and the like and the reactions are complete in from 1 to 24 hours at 0°C to the reflux temperature of the solution.

During certain reactions described below, it may be

10 necessary to protect the groups at R2, R3, R4, R8, R9 and R10. With these positions protected, the reactions may be carried out at other positions without affecting the remainder of the molecule. Subsequent to any of the described reactions (vide infra), the protecting group(s) may be removed and the unprotected product isolated. The protecting groups

15 employed at R2, R3, R4, R8, R9 and R10 are those which may be readily synthesized, not significantly affected by the reactions at the other positions, and may be removed without significantly affecting any other functionality of the molecule. One preferred type of protecting group is the tri-substituted silyl group, preferably the tri-loweralkyl silyl group or

20 di-loweralkyl-aryl silyl group. Especially preferred examples are the trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl and dimethylphenylsilyl groups.

The protected compound may be prepared with the appropriately substituted silyl trifluoromethanesulfonate or silyl halide,

25 preferably the silyl chloride. The reaction is carried out in an aprotic solvent such as methylene chloride, benzene, toluene, ethyl acetate, isopropyl acetate, tetrahydrofuran, dimethylformamide and the like. In order to minimize side reactions, there is included in the reaction mixture a base to react with the acid released during the course of the reaction.

30 Preferred bases are amines such as imidazole, pyridine, triethylamine or diisopropylethylamine and the like. The base is required in amounts equimolar to the amount of hydrogen halide liberated, however, generally several equivalents of the amine are employed. The reaction is stirred at

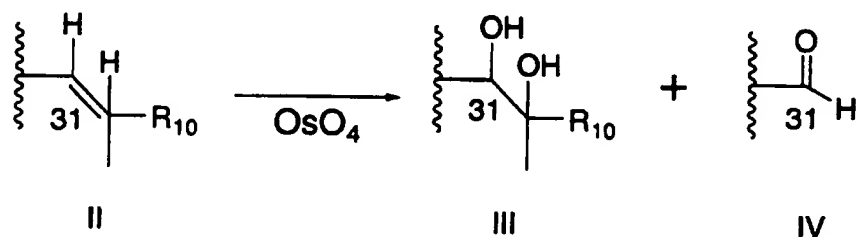
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oxo analog with  $H_2NNR^dCR^d$  to give the corresponding hydrazones using conditions directly analogous to those described for oxime formation.

Compounds of formula I wherein one or both of the ---- bonds represent a single bond may be prepared from the corresponding compound wherein ---- is a double bond by conventional hydrogenation procedures. The double bonds may be hydrogenated with any of a variety of standard precious metal hydrogenation catalysts such as Wilkinson's catalyst, Pearlman's catalyst, 1-25% palladium on carbon, 1-25% platinum on carbon and the like. The reaction is generally carried out in a non-reducible solvents (either protic or aprotic) such as methanol, ethanol, isopropanol, tetrahydrofuran, ethyl acetate, isopropyl acetate, benzene, toluene, dimethylformamide and the like. The hydrogen source may be hydrogen gas from 1 to 50 atmospheres of pressure or other hydrogen sources such as ammonium formate, cyclohexene, cyclohexadiene and the like. The reduction also may be carried out using sodium dithionite and sodium bicarbonate in the presence of a phase transfer catalyst, in particular a tetraalkylammonium phase transfer catalyst, and the like. The reactions may be run from 0°C to 100°C and are complete in from 5 min to 24 hours.

Compounds of formula I wherein R<sub>8</sub> and R<sub>9</sub> are both hydroxyl groups may be prepared according to the procedure shown in Scheme I.

## SCHEME I



Thus, Compound II is treated with osmium tetroxide under conditions known to those skilled in the art to yield the diol product III. Also produced during this reaction is the aldehyde IV. Osmium tetroxide may

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borohydride and the like. Compounds of formula I wherein R<sub>2</sub> and R<sub>1</sub> together are oxo and R<sub>10</sub> is CH<sub>2</sub>OH may be obtained by reacting the appropriate carboxylic acid (e.g., where R<sub>10</sub> is CO<sub>2</sub>H) with less reactive reducing agents such as diborane and the like.

- 5           Compounds of formula I wherein R<sub>2</sub> is OH and R<sub>1</sub> is other than H, may be prepared from the corresponding ketone by treating the appropriate oxo analog with a Grignard reagent R<sub>1</sub>MgBr, or with a lithium reagent R<sub>1</sub>Li. These reactions are performed in a manner known to those skilled in the art and preferably are performed in aprotic solvents  
10 such as diethyl ether, tetrahydrofuran, hexanes or pentanes. The reactions are complete in from 5 minutes to 24 hours at temperatures ranging from -78°C to 60°C.

- Compounds of formula I where R<sub>10</sub> is C(O)N(OR<sup>b</sup>)R<sup>c</sup> or C(O)NR<sup>c</sup>R<sup>d</sup> are prepared from the corresponding carboxylic acid using  
15 standard amide-forming reagents known to those skilled in the art. The reaction is carried out using at least one equivalent of an amine nucleophile, HN(OR<sup>b</sup>)R<sup>c</sup> or HNR<sup>c</sup>R<sup>d</sup>, although preferably ten to one hundred equivalents of amine nucleophiles are employed. Amide-forming reagents include, but are not restricted to,  
20 dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl), diisopropylcarbodiimide, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium  
25 hexafluorophosphate (PyBOP), chloro-tris-pyrrolidino-phosphonium hexafluorophosphate (PyCloP), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), diphenylphosphoryl azide (DPPA), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-benzotriazol-1-yl-N,N',N'-bis(pentamethylene)uronium  
30 hexafluorophosphate and 2-chloro-1-methylpyridinium iodide. The amide-forming reactions may be facilitated by the optional addition of N-hydroxybenzotriazole or N-hydroxy-7-aza-benzotriazole. The amidation reaction is generally performed using at least one equivalent (although several equivalents may be employed) of amine bases such as

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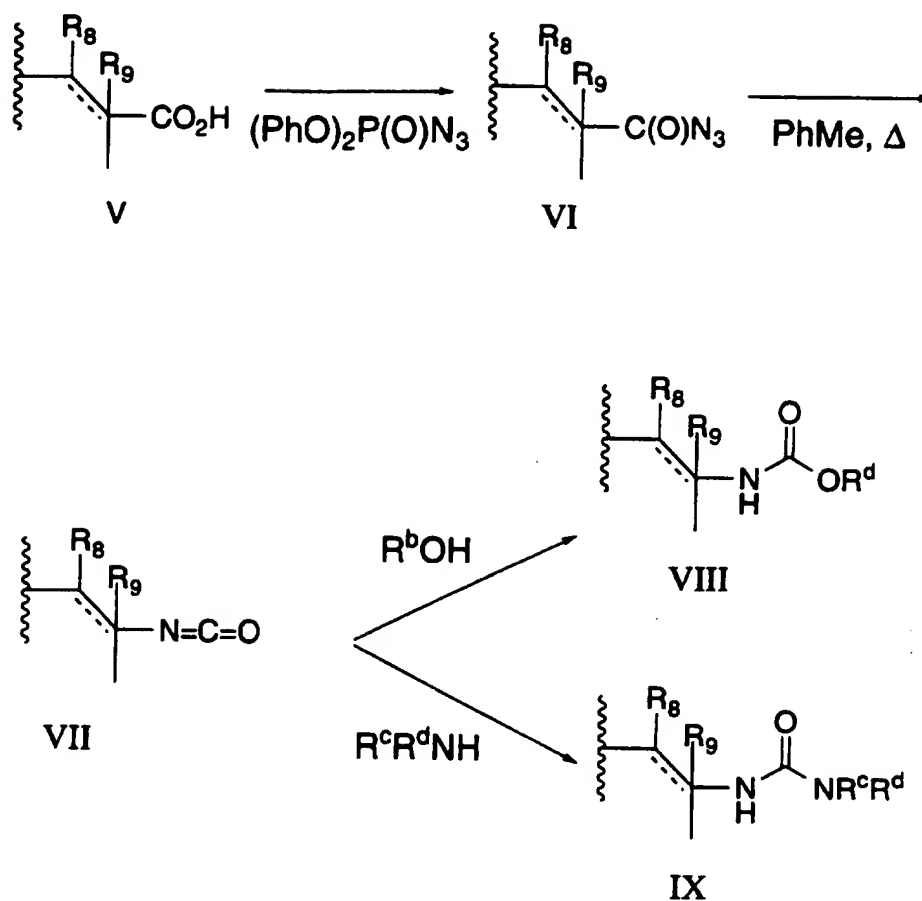
- hexafluorophosphate and 2-chloro-1-methylpyridinium iodide. The ester-forming reactions may be facilitated by the optional addition of N-hydroxybenzotriazole, N-hydroxy-7-aza-benzotriazole, 4-(N,N-dimethylamino)pyridine or 4-pyrrolidinopyridine. The reaction is
- 5 generally performed using at least one equivalent (although several equivalents may be employed) of amine bases such as triethylamine, diisopropylethylamine, pyridine and the like. The carboxyl group may be activated for ester bond formation via its corresponding acid chloride or mixed anhydride, using conditions known to those skilled in the art.
- 10 These ester-forming reactions are carried out in aprotic solvents such as methylene chloride, tetrahydrofuran, diethyl ether, dimethylformamide, N-methylpyrrolidine and the like at temperatures ranging from -20°C to 60°C and are complete in 15 minutes to 24 hours.

- Compounds of formula I wherein one or more of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>8</sub> and R<sub>9</sub> is OR<sup>a</sup>, OCO<sub>2</sub>R<sup>b</sup> or OC(O)NR<sup>c</sup>R<sup>d</sup>, and/or where R<sub>10</sub> is CH<sub>2</sub>OR<sup>a</sup>, CH<sub>2</sub>OCO<sub>2</sub>R<sup>b</sup> or CH<sub>2</sub>OC(O)NR<sup>c</sup>R<sup>d</sup> may be prepared using known methods for acylation, sulfonylation and alkylation of alcohols. Thus, acylation may be accomplished using reagents such as acid anhydrides, acid chlorides, chloroformates, carbamoyl chlorides,
- 20 isocyanates and amine bases according to general procedures known to those skilled in the art. Sulfonylations may be carried out using sulfonylchlorides or sulfonic anhydrides. The acylation and sulfonylation reactions may be carried out in aprotic solvents such as methylene chloride, chloroform, pyridine, benzene, toluene and the like. The
- 25 acylation and sulfonylation reactions are complete in from 15 minutes to 24 hours at temperatures ranging from -20°C to 80°C. The degree of acylation, sulfonylation and alkylation will depend on the amount of the reagents used. Thus, for example, using one equivalent of an acylating reagent and one equivalent of nodulisporic acid results in a product
- 30 mixture containing 4- and 20-acylated nodulisporic acid; such a mixture may be separated by conventional techniques such as chromatography.

Compounds of formula I wherein one or more of R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>8</sub> and R<sub>9</sub> is OR<sup>a</sup> and/or where R<sub>10</sub> is CH<sub>2</sub>OR<sup>a</sup>, may be prepared using methods known to those skilled in the art for the alkylation of



## SCHEME II



- 5 In Scheme II,  $\text{R}_8$ ,  $\text{R}_9$ ,  $\text{R}^b$ ,  $\text{R}^c$ ,  $\text{R}^d$  and ---- have the same meaning as defined under formula I. Thus, the carboxylic acid (compound V) is treated with diphenylphosphoryl azide to provide the acyl azide (compound VI). Heating of compound VI in an aprotic solvent such as benzene, toluene, dimethylformamide and the like results
- 10 in a rearrangement yielding compound VII, an isocyanate. Compound VII may be reacted in an aprotic solvent such as benzene, toluene, methylene chloride, 1,2-dichloroethylene, dimethylformamide and the like, with an alcohol  $\text{R}^b\text{OH}$ , such as methanol, ethanol, benzyl alcohol, 2-trimethylsilylethanol, 2,2,2-trichloroethanol, methyl glycolate, phenol
- 15 and the like to yield compound VIII, a carbamate. The addition of one or

and organs of the body such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like. The parasitic infections known as helminthiases lead to anemia, malnutrition, weakness, weight loss, severe damage to the walls of the intestinal tract and other tissues and organs and, if left untreated, may result in death of the infected host. The compounds of this invention have activity against these parasites, and in addition are also active against *Dirofilaria* in dogs and cats, *Nematospirides*, *Syphacia*, *Aspiculuris* in rodents, arthropod ectoparasites of animals and birds such as ticks, mites such as scabies lice, fleas, blowflies, and other biting insects in domesticated animals and poultry, such as *Tenophalides*, *Ixodes*, *Psoroptes*, and *Hemotobia*, in sheep *Lucilia* sp., biting insects and such migrating dipterous larvae as *Hypoderma* sp. in cattle, *Gastrophilus* in horses, and *Cuterebra* sp. in rodents and nuisance flies including blood feeding flies and filth flies.

The instant compounds are also useful against parasites which infect humans. The most common genera of parasites of the gastro-intestinal tract of man are *Ancylostoma*, *Necator*, *Ascaris*, *Strongyloides*, *Trichinella*, *Capillaria*, *Trichuris*, and *Enterobius*. Other medically important genera of parasites which are found in the blood or other tissues and organs outside the gastrointestinal tract are the filarial worms such as *Wuchereria*, *Brugia*, *Onchocerca* and *Loa*, *Dracunculus* and extra intestinal stages of the intestinal worms *Strongyloides* and *Trichinella*. The compounds are also of value against arthropods parasitizing man, biting insects and other dipterous pests causing annoyance to man.

The compounds are also active against household pests such as the cockroach, *Blatella* sp., clothes moth, *Tineola* sp., carpet beetle, *Attagenus* sp., the housefly *Musca domestica* as well as fleas, house dust mites, termites and ants.

The compounds are also useful against insect pests of stored grains such as *Tribolium* sp., *Tenebrio* sp. and of agricultural plants such as aphids, (*Acyrtosiphon* sp.); against migratory orthopterans such as locusts and immature stages of insects living on plant tissue. The compounds are useful as a nematocide for the control of soil nematodes

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boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate, or di-calcium phosphate.

Where it is desired to administer the instant compounds in a dry, solid unit dosage form, capsules, boluses or tablets containing the  
5 desired amount of active compound usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents, and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be  
10 varied widely with respect to their total weight and content of the antiparasitic agent depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the active compound is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top  
15 dressing or in the form of pellets or liquid which may then be added to the finished feed or optionally fed separately. Alternatively, feed based individual dosage forms may be used such as a chewable treat. Alternatively, the antiparasitic compounds of this invention may be administered to animals parenterally, for example, by intraruminal,  
20 intramuscular, intravascular, intratracheal, or subcutaneous injection in which the active ingredient is dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active material is suitably admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cotton seed oil and the like. Other parenteral  
25 vehicles such as organic preparation using solketal, glycerol formal, propylene glycol, and aqueous parenteral formulations are also used. The active compound or compounds are dissolved or suspended in the parenteral formulation for administration; such formulations generally contain from 0.0005 to 5% by weight of the active compound.

30 The agents of this invention can be used in the treatment and/or prevention of diseases caused by parasites, for example, arthropod parasites such as ticks, lice, fleas, mites and other biting arthropods in domesticated animals and poultry. The agents of this invention also are useful in the prevention and treatment of diseases caused by

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methods such as grinding, stirring, milling or tumbling. Compositions containing from about 0.005 to 2.0% weight of the active compound are particularly suitable as feed premixes. Feed supplements, which are fed directly to the animal, contain from about 0.0002 to 0.3% by weight of the active compounds.

Such supplements are added to the animal feed in an amount to give the finished feed the concentration of active compound desired for the treatment and control of parasitic diseases. Although the desired concentration of active compound will vary depending upon the factors previously mentioned as well as upon the particular compound employed, the compounds of this invention are usually fed at concentrations of between 0.00001 to 0.002% in the feed in order to achieve the desired anti-parasitic result.

In using the compounds of this invention, the individual compounds may be prepared and used in that form. Alternatively, mixtures of the individual compounds may be used, or they may be combined with other active compounds not related to the compounds of this invention.

The compounds of this invention are also useful in combatting agricultural pests that inflict damage upon crops while they are growing or while in storage. The compounds are applied using known techniques as sprays, dusts, emulsions and the like, to the growing or stored crops to effect protection from such agricultural pests.

Compounds of this invention may be co-administered with anthelmintic agents. These anthelmintic agents are meant to include, but not be restricted to, compounds selected from the avermectin and milbemycin class of compounds such as ivermectin, avermectin, abamectin, emamectin, eprinamectin, doramectin, fulladectin, moxidectin, Interceptor and nemadectin. Additional anthelmintic agents include the benzimidazoles such as thiabendazole, cambendazole, parbendazole, oxibendazole, mebendazole, flubendazole, fenbendazole, oxfendazole, albendazole, cyclobendazole, febantel, thiophanate and the like. Additional anthelmintic agents include imidazothiazoles and

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To 0.8 mg Compound B in 1 mL methanol at room temperature was added 0.2 mL 1 M trimethylsilyldiazomethane in hexanes. After 5 minutes, 0.1 mL glacial acetic acid was added, the solution stirred for three minutes and the 2 mL saturated NaHCO<sub>3</sub> was added (foaming occurred). The solution was extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 15:85 water/methanol as eluant and the purified product was characterized by <sup>1</sup>H NMR.

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## EXAMPLE 3

Methyl 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydronodulisporate

To 1 mg Compound C in 1 mL methanol at room temperature was added 0.2 mL 1 M trimethylsilyldiazomethane in hexanes. After 5 minutes, 0.1 mL glacial acetic acid was added, the solution stirred for three minutes and the 2 mL saturated NaHCO<sub>3</sub> was added (foaming occurred). The solution was extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 17.5:82.5 water/methanol as eluant and the purified product was characterized by <sup>1</sup>H NMR.

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

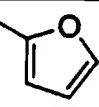
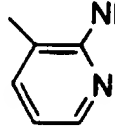
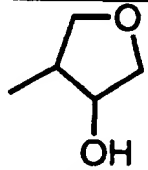
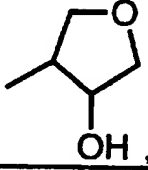
## EXAMPLE 4

Ethyl nodulisporate

To a solution containing 20 mg nodulisporic acid in 2 mL methylene chloride at room temperature was added 0.11 mL ethanol, 0.008 mL diisopropylethylamine, 1 mg N,N-dimethylaminopyridine (DMAP) followed by 13 mg BOP reagent. After 50 hours at room temperature, the solution was poured into 1/1 saturated sodium bicarbonate/brine and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, the solids were removed by filtration and the solution concentrated under reduced pressure. Pure product was obtained following preparative TLC on silica gel (one 1000 micron plate) using 1/3 acetone/hexanes as eluant. Purified product (15

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14	815.4	4-Nitrobenzyl alcohol	$\text{CH}_2\text{Ph}(4\text{-NO}_2)$
15	815.4	3-Nitrobenzyl alcohol	$\text{CH}_2\text{Ph}(3\text{-NO}_2)$
16	807.7	2-Hydroxy-3-(1-pyrrolidinyl)propanol	$\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{-N}$ 
17	793.7	4-(2-Hydroxyethyl)-morpholine	$\text{CH}_2\text{CH}_2\text{-N}$ 
18	762.4	2,2,2-Trifluoroethanol	$\text{CH}_2\text{CF}_3$
19		2-(Hydroxymethyl)furan	$\text{CH}_2$ 
20	764.5	5-Hydroxypentan-2-one	$\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{CH}_3$
21		3-Phenylpropanol	$\text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}$
22	764.3	3,3-Dimethylbutanol	$\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_3$
23		2-(N-Acetylamino)-3-hydroxypyridine	
24	766.7	3,4-Dihydroxytetrahydrofuran, Isomer A	 OH, isomer A
25	766.6	3,4-Dihydroxytetrahydrofuran, Isomer B	 OH, isomer B
26	831.5	1,1,1,3,3,3-hexafluoroisopropanol	$\text{CH}(\text{CF}_3)_2$
27		2-(Trifluoromethyl)benzyl alcohol	$\text{CH}_2\text{Ph}(2\text{-CF}_3)$

## EXAMPLE 28

General Procedure for the Preparation of Additional Ester Derivatives of Compounds A, B and C

- (hydroxymethyl)propanol, trans-2-Hydroxycyclohexanol, 2-Hydroxy-4-methylphenol, 2-(Hydroxymethyl)pyridine, 1-Hydroxymethyl-1-cyclohexanol, 2-Hydroxyhexanol, 2-Hydroxy-1-methoxypropane, 2-(Hydroxymethyl)imidazole, 3-Hydroxymethylpyrazole, trans-4-
- 5 Hydroxycyclohexanol, N-Acetyl-4-hydroxybutylamine, Hydroxycyclopentane, 2-(Methylsulfonyl)ethanol, 2-(Methylsulfinyl)ethanol, 4-(2-Hydroxyethyl)phenol, 2-(2-Hydroxyethyl)phenol, 2-Hydroxy-3-methylbutanol, 3-(N-Acetyl-amino)propanol, 3-(Diethylamino)propanol, 3-
- 10 (Dimethylamino)propanol, Allyl alcohol, 2-(Dimethylamino)ethanol, Glycerol, 2-Methoxyethanol, 2-(N-Acetyl-amino)ethanol, D-(Hydroxymethyl)pyrrolidine, 3-Hydroxypyrrolidine, 2-(Hydroxyethyl)benzene, 2-Hydroxyethyl-1-methylpyrrolidine, 2-Hydroxy-2-methyl-propanol, Cyclopropanol, Cyclohexanol, 3-
- 15 Hydroxypropanol, 3-Ethoxypropanol, Propargyl alcohol, Ethyl glycolate, 2-Fluoroethanol, 3-(Dodecyloxy)propanol, 4-Hydroxybutanol, 5-Hydroxypentanol, 2-(Dimethylamino)ethanol, 2-(2-Hydroxyethoxy)ethanol, 1-(2-Hydroxyethyl)imidazolone, 2-(2-Hydroxyethoxy)ethylamine, Isopropanol, 2,2,2-Trifluoroethanol, 4-
- 20 Nitrobenzyl alcohol, 3-Nitrobenzyl alcohol, 2-Methoxyethanol, 4-(Hydroxyethyl)phenol, 4-(3-Hydroxypropyl)-1-sulfonamidobenzene, D,L-2-(Hydroxymethyl)tetrahydrofuran, Methyl lactate, 5-Hydroxyhexanoic acid, methyl ester, 3-Methoxypropanol, 3-Hydroxypiperidine, Pentanol, 4-Hydroxyheptane, 4-(2-Hydroxyethyl)-
- 25 1,2-dimethoxybenzene, 4-Hydroxymethyl-1,2-methylenedioxybenzene, 4-(Trifluoromethyl)benzyl alcohol, 4-(Methylthio)pheno, 2-(Hydroxymethyl)furan, 5-Hydroxypentan-2-one, 2-Hydroxy-3-methylbutanoic acid, methyl ester, 2-Hydroxy-3-phenyl-propanoic acid, ethyl ester, 1-(Hydroxymethyl)napthalene, 3-Phenylpropanol, 3,3-
- 30 Dimethylbutanol, 3-(2-Hydroxyethyl)fluorobenzene, 4-Hydroxy-1-carboethoxypiperidine, (R)-2-(Hydroxymethyl)tetrahydrofuran, (S)-2-(Hydroxymethyl)tetrahydrofuran, (S)-2-Hydroxy-3-methylbutanol, (R)-2-Hydroxy-3-methylbutanol, (S)-2-Hydroxy-propanol, 3,4-Dihydroxytetrahydrofuran, 1,1,1,3,3,3-hexfluoroisopropanol, 2-

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After 30 minutes at room temperature, the reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude was partially purified by silica gel flash chromatography using 0.5:5:95  $\text{NH}_4\text{OH}/\text{MeOH}/\text{CHCl}_3$  as eluant followed by reversed-phase HPLC purification using 20:80 water/methanol as eluant. The product was characterized by  $^1\text{H}$  NMR.

### EXAMPLE 31

#### 4-Morpholinyl-nodulisporamide

10

To 1.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop morpholine and 2 mg N-hydroxybenzotriazole. 2 mg pyBOP was then added. After 1 hour at room temperature, the solution was filtered through 2 inches silica gel in a pipet without workup using ethyl acetate as eluant. The resultant solution was concentrated under reduced pressure and pure product was obtained following reversed-phase HPLC using 20:80 water/MeOH as eluant. The product was characterized by  $^1\text{H}$  NMR.

20

### EXAMPLE 32

#### N-(2-Hydroxyethyl)-nodulisporamide

To 0.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 2 drops diisopropylethylamine, 5 mg  $\text{H}_2\text{NCH}_2\text{CH}_2\text{OH}$ , 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 30 minutes, the reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 20:80 water/methanol as eluant and the product was characterized by  $^1\text{H}$  NMR and mass spectrometry.

30

### EXAMPLE 33

#### N-(1-Methoxycarbonyl-2-hydroxyethyl)-nodulisporamide



17.5:82.5 water/methanol as eluant. The product was characterized by  $^1\text{H}$  NMR and mass spectrometry.

#### EXAMPLE 36

##### 5 N,N-Tetramethylene-nodulisporamide

To 125 mg nodulisporic acid in 10 mL methylene chloride at 0°C was added 0.18 mL diisopropylethylamine, 0.15 mL pyrrolidine followed by 108 mg PyBOP. After 5 minutes, the solution was warmed  
10 to room temperature. After 1.5 hours, the solution was poured in 25 mL saturated  $\text{NaHCO}_3$ , extracted with methylene chloride, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Pure N,N-tetramethylene-nodulisporamide was obtained following reversed-phase HPLC purification using 50:50 acetonitrile/water as eluant (isocratic for  
15 ten min), followed by a linear 30 minute gradient to 75:25 acetonitrile/water. Pure product (26 mg) was characterized by  $^1\text{H}$  NMR and MS.

#### EXAMPLE 37

##### 20 N-Ethyl 29,30-dihydro-20,30-oxa-nodulisporamide

To 1 mg Compound B in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop  $\text{CH}_3\text{CH}_2\text{NH}_2$ , 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 15  
25 minutes, the reaction was quenched with 2 mL saturated  $\text{NaHCO}_3$ , extracted with ethyl acetate, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 15:85 water/methanol as eluant and the purified product was  
30 characterized by  $^1\text{H}$  NMR.

#### EXAMPLE 38

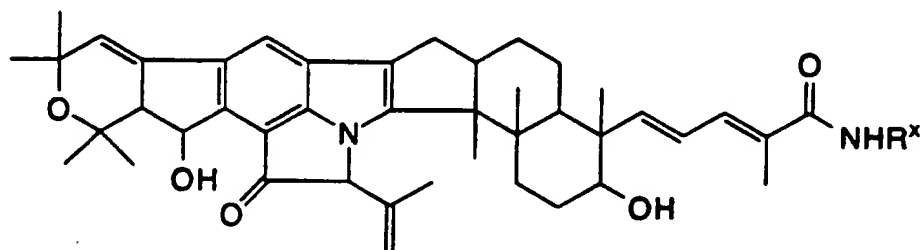
##### N-(2-Hydroxyethyl)-29,30-dihydro-20,30-oxa-nodulisporamide

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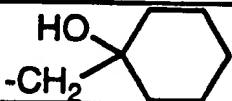
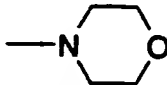
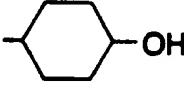
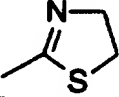
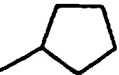
on silica gel (one 1000 micron plate) using 1/2 acetone/hexanes as eluant. Additional purification using HPLC (6/4 acetonitrile/water for 15 minutes, then a 45 minute linear gradient to 7/3 acetonitrile/water) yielded pure product (17 mg). The purified product was characterized by proton NMR and MS ( $m/z$ : 735.7 ( $M+1$ )).

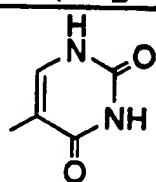
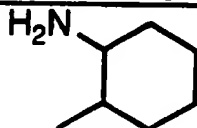
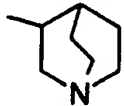
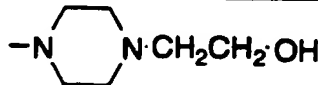

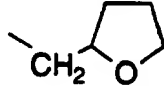
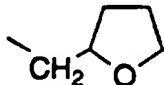
The general procedure of Example 40 was repeated using the appropriate amines listed in Table 3 below to provide the corresponding monosubstituted nodulisporamide compounds. These compounds were characterized by proton NMR and/or mass spectrometry (unless otherwise specified,  $m/z$  is for  $M+1$ ).

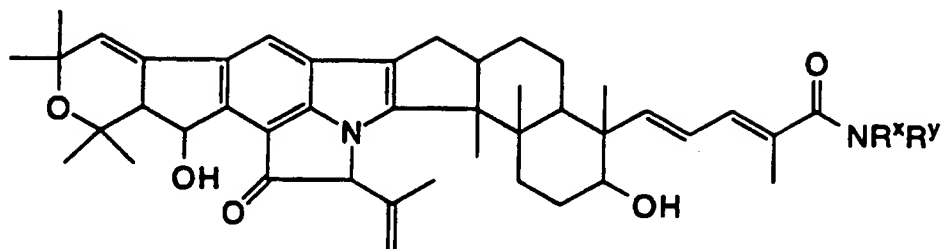
Table 3: Monosubstituted Aliphatic Nodulisporamide Derivatives



Ex.	$m/z$	Amines	$R^x$
41	796.5	Aminoacetaldehyde diethyl acetal	$\text{CH}_2\text{CH}(\text{OCH}_2\text{CH}_3)_2$
42	767.6	(2-Hydroxyethoxy)-ethylamine	$\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$
43	792.5	4-(2-Aminoethyl)-morpholine	$-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{O}$
44	790.4	1-(2-Aminoethyl)-piperidine	$-\text{CH}_2\text{CH}_2-\text{N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array}$
45	807.5	6-Amino-2-methylheptan-2-ol	$\text{CH}(\text{CH}_3)(\text{CH}_2)_3\text{C}(\text{CH}_3)_2\text{OH}$
46	737.5	3-Aminopropanol	$(\text{CH}_2)_3\text{OH}$

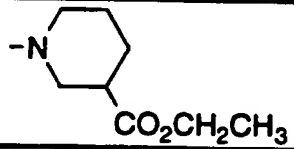
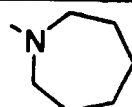
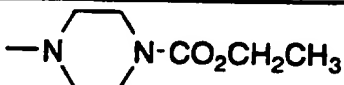
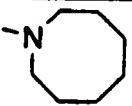
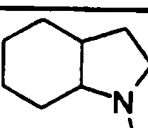
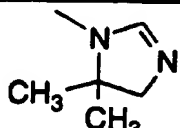
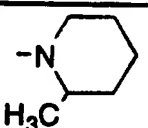
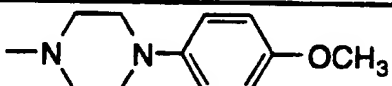
67	766.5	2-(2-Aminoethylamino)-ethanol	$\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OH}$
68	791.4	1-Aminomethyl-cyclohexan-1-ol	
69	779.4	2-Aminoethanol	$\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2)_3\text{CH}_3$
70	751.5	2-Amino-1-methoxypropane	$\text{CH}(\text{CH}_2\text{OCH}_3)\text{CH}_3$
71	764.4	4-Aminomorpholine	
72	777.6	trans-4-Aminocyclohexan-1-ol	
73	739.4	2-Aminoethanethiol	$(\text{CH}_2)_2\text{SH}$
74	750.5	4-Aminobutylamine	$(\text{CH}_2)_4\text{NH}_2$
75	764.4	2-Amino-4,5-dihydrothiazole	
76	747.5	Aminocyclopentane	
77		2-(Methylsulfonyl)-ethylamine	$\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$
78		2-(Methylsulfinyl)-ethylamine	$\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$
79	765.4	2-Amino-3-methylbutanol	$\text{CH}(\text{CH}(\text{CH}_3)_2)\text{CH}_2\text{OH}$
80	736.5	3-Aminopropylamine	$(\text{CH}_2)_3\text{NH}_2$
81	792.5	3-(Diethylamino)-propylamine	$(\text{CH}_2)_3\text{N}(\text{CH}_2\text{CH}_3)_2$
82	764.5	3-(Dimethylamino)-propylamine	$(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$
83	723.5	O-Ethylhydroxylamine	$\text{OCH}_2\text{CH}_3$
84	753.5	3-Amino-2-hydroxypropanol	$\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$
85	709.4	O-Methylhydroxylamine	$\text{OCH}_3$
86	737.4	2-Methoxyethylamine	$\text{CH}_2\text{CH}_2\text{OCH}_3$

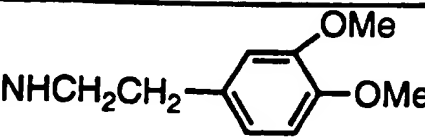
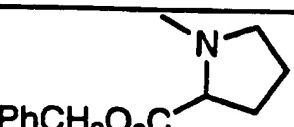
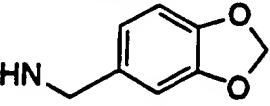
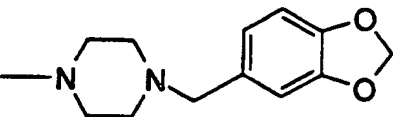
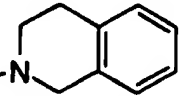
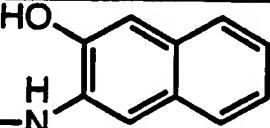
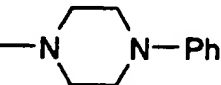
107	777.5	4-Amino-4-methyl-pentan-2-one	$C(CH_3)_2CH_2C(O)CH_3$
108	837.6	Diethyl 2-aminomalonate	$CH(CO_2CH_2CH_3)_2$
109		5-Aminouracil	
110	707.6	Ethylamine	$CH_2CH_3$
111	807.8	Norleucine methyl ester	$CH(CH_2CH_2CH_3)CO_2CH_3$
112	751.7	3-Methoxypropylamine	$CH_2CH_2CH_2OCH_3$
113	745.5	1,1-Dimethylpropargyl-amine	$C(CH_3)_2C\equiv CH$
114	749.7	Pentylamine	$(CH_2)_4CH_3$
115	777.9	4-Aminoheptane	$CH(CH_2CH_2CH_3)_2$
116	763.8	Hexylamine	$(CH_2)_5CH_3$
117	776.8	cis-1,2-Diaminocyclohexane	
118	788.9	3-Aminoquinuclidine	
119	751.7	beta-Alanine	$CH_2CH_2CO_2H$
120	793.5	L-Valine methyl ester	$CH(CH(CH_3)_2)CO_2CH_3$
121		1-Amino-4-(2-Hydroxyethyl)piperazine	
122	753.4	Aminooxyacetic acid	$OCH_2CO_2H$
123	834.5	4-Amino-1-carboethoxypiperidine	
124	763.5	(R)-2-(Aminomethyl)-tetrahydrofuran	
125	763.6	(S)-2-(Aminomethyl)-tetrahydrofuran	

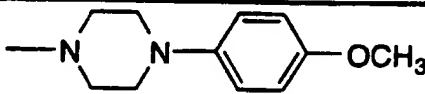
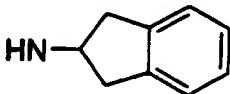
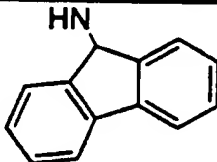
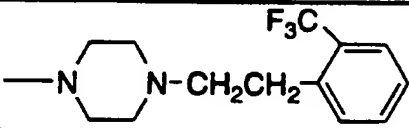


Ex.	m/z	Amine	NR <sup>x</sup> R <sup>y</sup>
144	791.5	1-(2-Aminoethyl)-piperazine	
145	776.6	4-Aminomethylpiperidine	
146	765.4	Thiomorpholine	
147	759.4	Diallylamine	N(CH <sub>2</sub> CH=CH <sub>2</sub> ) <sub>2</sub>
148	737.4	2-(Methylamino)ethanol	N(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>2</sub> OH
149	795.4	Diisopropanolamine	N(CH <sub>2</sub> CH(CH <sub>3</sub> )OH) <sub>2</sub>
150	763.5	L-2-(Hydroxymethyl)-pyrrolidine	
151	763.5	D-2-(Hydroxymethyl)-pyrrolidine	
152	749.5	3-Hydroxypyrrolidine	
153	732.7	Methylaminoacetonitrile	N(CH <sub>3</sub> )CH <sub>2</sub> C≡N
154		4-(2-hydroxyethyl)-piperazine	
155	777.7	4-Ethylpiperazine	
156	721.5	N-Ethylmethylamine	N(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>
157	735.6	N-(Methyl)isopropylamine	N(CH <sub>3</sub> )CH(CH <sub>3</sub> ) <sub>2</sub>



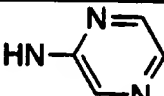
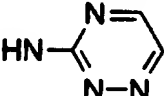
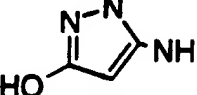
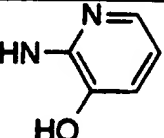
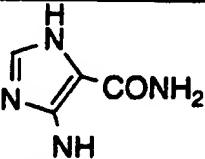
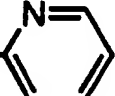
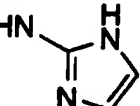
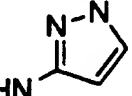
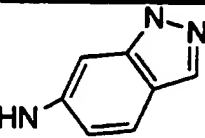
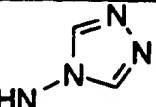
- 57 -

175	819.6	3-(Carboethoxy)piperidine	
176	761.6	Hexamethyleneimine	
177	820.7	1-(Carboethoxy)piperazine	
178	819.7	Dipentylamine	$N(CH_2CH_2CH_2CH_2CH_3)_2$
179	775.6	Heptamethyleneimine	
180	787.6	Octahydroindole	
181	760.5	4,5-Dihydro-5,5-dimethylimidazole	
182	707.5	Dimethylamine	$N(CH_3)_2$
183	763.7	Dipropylamine	$N(CH_2CH_2CH_3)_2$
184	761.7	2-Methylpiperidine	
185	779.5	2-(Butylamino)ethanol	$N((CH_2)_2CH_3)CH_2CH_2OH$
186	731.7	Methylpropargylamine	$N(CH_3)CH_2C\equiv CH$
187	854.7	1-(4-Methoxyphenyl)-piperazine	
188	931.9	Dinonylamine	$N((CH_2)_8CH_3)_2$
189	903.8	Dioctylamine	$N((CH_2)_7CH_3)_2$

212	843.8	4-(2-Aminoethyl)-1,2-dimethoxybenzene	$\text{NHCH}_2\text{CH}_2$ - 
213	867.5	L-Proline benzyl ester	$\text{PhCH}_2\text{O}_2\text{C}$ - 
214	813.8	4-Aminomethyl-1,2-methylenedioxybenzene	$\text{HN}$ - 
215	837.5	4-(Trifluoromethyl)-benzylamine	$\text{NHCH}_2\text{Ph}(4\text{-CF}_3)$
216	882.6	1-((3,4-methylenedioxy)-benzyl)piperazine	- 
217	862.7	3-(Benzyloxy)aniline	$\text{NHPh}(4\text{-OCH}_2\text{Ph})$
218	801.4	4-(Methylthio)aniline	$\text{NHPh}(4\text{-SCH}_3)$
219	855.5	L-Phenylalanine ethyl ester	$\text{NHCH}(\text{CH}_2\text{Ph})\text{CO}_2\text{CH}_2\text{CH}_3$
220	841.4	D-Phenylalanine methyl ester	$\text{NHCH}(\text{CH}_2\text{Ph})\text{CO}_2\text{CH}_3$
221	799.4	4-(Methoxy)benzylamine	$\text{NHCH}_2\text{Ph}(4\text{-OCH}_3)$
222	819.5	1-(Aminomethyl)naphthalene	$\text{NHCH}_2$ -1-naphthyl
223	792.4	1,2,3,4-Tetrahydro-isoquinoline	- 
224	821.8	3-Amino-2-hydroxy-naphthalene	
225	801.7	3-(2-Aminoethyl)-fluorobenzene	$\text{NHCH}_2\text{CH}_2(3\text{-F})\text{Ph}$
226	823.7	4-Phenylpiperazine	- 
227	814.7	D-Phenylalaninol	$\text{NHCH}(\text{CH}_2\text{Ph})\text{CH}_2\text{OH}$

247	812.7	N-Methyl-N-phenyl-ethylenediamine	$\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{Ph}$
248	837.6	3-(Trifluoromethyl)-benzylamine	$\text{NHCH}_2\text{Ph}(3\text{-CF}_3)$
249	837.7	2-(Trifluoromethyl)-benzylamine	$\text{NHCH}_2\text{Ph}(2\text{-CF}_3)$
250		1-(4-Methoxyphenyl)-piperazine	
251	795.7	2-Aminoindane	
252	843.6	9-Aminofluorene	
253	811.7	4-Phenylbutylamine	$\text{NH}(\text{CH}_2)_4\text{Ph}$
254	827.8	(R,R)-2-Methylamino-3-phenylbutane	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
255	827.8	(S,S)-2-Methylamino-3-phenylbutane	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
256	825.9	Benzylbutylamine	$\text{N}(\text{CH}_2\text{Ph})(\text{CH}_2)_3\text{CH}_3$
257	785.6	O-Benzylhydroxylamine	$\text{NHCH}_2\text{Ph}$
258	805.5	2,6-Difluorobenzylamine	$\text{NCH}_2\text{Ph}(2,6\text{-diF})$
259	920.9	1-(2-(o-Trifluoromethyl-phenyl)ethyl)piperazine	
260	797.7	(S)-N, alpha-Dimethylbenzylamine	$\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$
261	783.7	(S)-alpha-Methylbenzylamine	$\text{NHCH}(\text{CH}_3)\text{Ph}$
262	797.6	Methyl benzyl amine	$\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$
263		4-Aminomethyl-1,2-dichlorobenzene	$\text{NHCH}_2\text{Ph}(3,4\text{-diCl})$



281	787.5	1-(3-Aminopropyl)-imidazole	HN-(CH <sub>2</sub> ) <sub>3</sub> 
282	770.6	4-(Aminomethyl)pyridine	-NHCH <sub>2</sub> - 
283	757.4	2-Aminopyrazine	HN- 
284		3-Amino-1,2,4-triazine	HN- 
285		5-Amino-3-hydroxypyrazole	
286		2-Amino-3-hydroxypyridine	HN- 
287		4-Amino-5-carboxamidoimidazole	
288	770.4	2-(Aminomethyl)pyridine	-NHCH <sub>2</sub> - 
289	751.5 M+Li	2-Aminoimidazole	HN- 
290	745.4	3-Aminopyrazole	HN- 
291	795.2	6-Aminobenzopyrazole	HN- 
292	797.5	4-Amino-1,2,4-triazole	HN- 

### General Procedure for the Preparation of Additional Amide Derivatives of Nodulisporic Acid

To a solution of 30 mg of nodulisporic acid in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of amine selected from Table 5. Stir the solution overnight at 4 °C and then pour into 1/1 saturated sodium bicarbonate/brine, extract with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution to dryness under reduced pressure. Pure product may be obtained by flash chromatography or preparative TLC on silica gel or reversed-phase liquid chromatography. The purified product may be characterized by proton NMR and mass spectrometry.

15

Table 5: Amines for the Preparation of Additional Nodulisporamide Derivatives

N-Methyl-2,2,2-trifluoroethylamine, 2,2,3,3,3-Pentafluoropropylamine, N-Methyl-2,2,3,3,3-pentafluoropropylamine, 1,1,1,3,3,3-Hexafluoroisopropylamine, 2-Difluoro-3-Methoxy-1-methyl-propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine, 1,1,1-Trifluoromethylpropylamine, 2-(3,3,3-Trifluoromethyl)propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine, Di-(2,2,2-trifluoroethyl)amine, N-(2-Methoxyethyl)-2,2,2-trifluoroethylamine, 2-Methoxy-1-methyl-ethylamine, 3-Methoxy-1-methyl-propylamine, 2-Methoxy-1-methyl-ethylamine, N-Methyl-2-methoxy-1-benzyl-ethylamine, 1-Methoxymethyl-3-methyl-butylamine, Methylsulfonamide, Isopropylsulfonamide, Ethylsulfonamide, Benzylsulfonamide, sec-Butylsulfonamide, N-Methyl-ethylsulfonamide, N,1,1-Trimethyl-propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine, 1-Methyl-propargylamine, 1-Trifluoromethylpropargylamine, N,1,1-Trimethyl-propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine,

- phenethylamine, 4-(2-Methoxyethyl)phenethylamine, 4-(Ethoxymethyl)phenethylamine, 4-(Acetoxyoxymethyl)phenethylamine, 3-(Dimethylaminomethyl)phenethylamine, 1-Phenyl-2,2,2-trifluoroethylamine, 4-(Trifluoromethoxy)aniline, 4-Methoxyaniline, 4-Ethoxyaniline, 3-Chloro-4-fluoro-aniline, 4-Chloro-2-fluoro-aniline, 4-(Acetoxy)aniline, 4-(Butoxy)aniline, 3-Chloroaniline, 4-(Methylthio)aniline, 5-(Aminomethyl)benzofuran, 5-(Methylaminomethyl)benzofuran, 4-(1-Aminoethyl)benzofuran, 5-(2-Aminoethyl)benzofuran, 5-Aminomethyl-2,3-dihydro-benzofuran, 5-Methylaminomethyl-2,3-dihydro-benzofuran, 4-1-Aminoethyl-2,3-dihydro-benzofuran, 5-2-Aminoethyl-2,3-dihydro-benzofuran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-1-Aminoethyl-2H-tetrahydrobenzopyran, 5-2-Aminoethyl-2H-tetrahydrobenzopyran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-(1-Aminoethyl)-2H-tetrahydrobenzopyran, 5-(2-Aminoethyl)-2H-tetrahydrobenzopyran, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-1-Aminoethyl-benzo-1,4-dioxane, 5-2-Aminoethyl-benzo-1,4-dioxane, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-(1-Aminoethyl)-benzo-1,4-dioxane, 5-(2-Aminoethyl)-benzo-1,4-dioxane, 3-Amino-5-methoxy-thiophene, 2-Amino-5-chloro-thiophene, 2-(2-Aminoethyl)thiophene, 2-(3-Aminopropyl)thiophene, 3-(3-Aminopropyl)thiophene, 3-(2-Methylaminoethyl)thiophene, 2-Chloro-3-(2-aminoethyl)-thiophene, 2-Aminoethyl-4-methoxy-thiophene, 2-Amino-3-ethyl-thiophene, 2-(Methylaminomethyl)thiophene, 3-(Aminomethyl)thiophene, 2-(2-Aminoethyl)-4-methoxy-thiophene, 1-(Aminomethyl)tetrazole, 1-(1-Aminoethyl)tetrazole, 1-(3-Aminopropyl)tetrazole, 5-Amino-3-methyl-isoxazole, 3-Aminopyridine, 4-Aminomethylthiazole, 2-(2-Aminoethyl)pyrazine, 2-(1-Aminoethyl)imidazole, 2-(Aminomethyl)isoxazole, 3-(2-Aminoethyl)pyrazole, 2-(Aminomethyl)-1,3,4-thiadiazole.

## EXAMPLE 304

- 2-(Methanesulfinyl)ethylamine, 4-(2-Hydroxyethyl)aniline, 2-(2-Hydroxyethyl)aniline, 2-Amino-3-methylbutanol, Diallylamine, 2-(Methylamino)ethanol, O-Ethylhydroxylamine, 3-Amino-2-hydroxypropanol, O-Methylhydroxylamine, L-
- 5 (Hydroxymethyl)pyrrolidine, 2-Methoxyethylamine, N-Acetylenediamine, D-(Hydroxymethyl)pyrrolidine, 3-Hydroxypyrrolidine, 2-(Aminoethyl)benzene, 2-Amino-2-methylpropanol, Cyclohexylamine, 3-Ethoxypropylamine, Allylamine, 2-Amino-2-hydroxymethyl-butanol, Propargylamine, 2-Fluoroethylamine,
- 10 3-(Dimethylamino)aniline, 2-Dimethylaminoethanol, 4-(2-hydroxyethyl)piperazine, 4-Ethylpiperazine, N-Ethylmethylamine, N-(Methyl)isopropylamine, 2,2,2-Trifluoroethylamine, N-Methylpropylamine, N-Methylbutylamine, N-Ethyl-2-methoxyethylamine, 4-(Aminoethyl)phenol, N-Methyl-2-
- 15 methoxyethylamine, N-Ethylpropylamine, D,L-2-(Aminomethyl)tetrahydrofuran, 1-Aminopiperidine, D-Alanine methyl ester, 3,5-Diamino-1,2,4-triazole, Benzylsulfonamide, 4-Amino-4-methyl-pentan-2-one, 5-Aminouracil, Ethylamine, Norleucine methyl ester, 3-Methoxypropylamine, 3-Hydroxypiperidine, 4-
- 20 Hydroxypiperidine, 1,1-Dimethylpropargylamine, N-(Ethyl)isopropylamine, Pentylamine, Piperidine, 2-Fluorophenylhydrazine, Hexylamine, Diethylamine, 4-(2-Aminoethyl)-1,2-dimethoxybenzene, 1-(2-Pyridyl)piperazine, 4-Methylpiperazine, 4-(2-Hydroxyethyl)morpholine, 4-Aminomethyl-1,2-
- 25 methylenedioxybenzene, 1-((3,4-methylenedioxy)benzyl)piperazine, 4-(Ethylaminomethyl)pyridine, L-Valine methyl ester, D-Phenylalanine methyl ester, 4-(Methoxy)benzylamine, 1-Amino-4-(2-hydroxyethyl)piperazine, 1,2,3,6-Tetrahydropyridine, 3-(2-Aminoethyl)fluorobenzene, 1-Phenylpiperazine, 4-Amino-1-
- 30 carboethoxypiperidine, 1-(Carboethoxy)piperazine, (R)-2-(Aminomethyl)tetrahydrofuran, (S)-2-(Aminomethyl)tetrahydrofuran, L-Valinol, D-Valinol, L-Alaninol, D-Phenylalaninol, 3,4-Dihydroxytetrahydrofuran, D-Alaninol, 2-Fluorobenzylamine, 4-Fluoroaniline, Isopropylamine, tert-Butylamine, iso-Butylamine, 4-(2-

- Trifluoromethylamino-4-pentyne, N-(2-Methoxyethyl)-2-amino-1,1-dimethyl-2-butyne, 1-Amino-2-butyne, 1-Amino-3-butyne, N-Methylamino-2-butyne, N-Methylamino-3-butyne, 1-Ethylamino-3-butyne, 2-(Aminomethyl)dioxane, 2-(2-Aminoethyl)dioxane, 2-(3-Aminopropyl)dioxane, 2-(2-Aminopropyl)dioxane, 2-(Methylaminomethyl)dioxane, 2-(1-Aminoethyl)dioxane, 2-Aminomethyl-2H-tetrahydropyran, 2-(2-Aminoethyl)-2H-tetrahydropyran, 2-(3-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminoethyl)-5-ethyl-2H-tetrahydropyran, 2-Methylaminomethyl-2H-tetrahydropyran, 2-(1-Aminoethyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)tetrahydrofuran, 2-Aminomethyl-5-ethyl-tetrahydrofuran, 2-Methylaminomethyl-tetrahydrofuran, 2-(Ethylaminomethyl)tetrahydrofuran, 2-(1-Aminoethyl)tetrahydrofuran, 4-(Methoxymethyl)benzylamine, 4-(2-Methoxyethyl)benzylamine, 4-(Ethoxymethyl)benzylamine, 4-(Acetoxymethyl)benzylamine, 3-(Dimethylaminomethyl)benzylamine, 4-(Sulfonamidomethyl)benzylamine, 2-Chloro-6-fluoro-benzylamine, 3-Chloro-4-fluoro-benzylamine, 2-Chloro-4-fluoro-benzylamine, 3,5-Difluoro-benzylamine, 2,4-Difluoro-benzylamine, Pentafluorobenzylamine, 4-Methoxy-2,3,5,6-tetrafluorobenzylamine, 4-(Methyl)benzylamine, Benzylamine, 4-(Ethyl)benzylamine, 4-(Ethoxy)benzylamine, 4-(Isopropyl)benzylamine, 4-(Isobutyl)benzylamine, 4-(Isopropoxy)benzylamine, 4-(Isobutoxy)benzylamine, 4-(Allyl)benzylamine, 4-(Allyloxy)benzylamine, 4-(3,3,1,1-Tetrafluoroallyloxy)benzylamine, 4-(Trifluoromethoxy)benzylamine, 4-(2,2,2-trifluoroethoxy)benzylamine, 3,4-Ethylenedioxybenzylamine, 4-Methoxymethyl-2-chloro-phenethylamine, 4-(2-Methoxyethyl)phenethylamine, 4-(Ethoxymethyl)phenethylamine, 4-(Acetoxymethyl)phenethylamine, 3-(Dimethylaminomethyl)phenethylamine, 1-Phenyl-2,2,2-trifluoroethylamine, 4-(Trifluoromethoxy)aniline, 4-Methoxyaniline, 4-Ethoxyaniline, 3-Chloro-4-fluoro-aniline, 4-Chloro-2-fluoro-aniline, 4-(Acetoxy)aniline, 4-(Butoxy)aniline, 3-Chloroaniline, 4-

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room temperature, extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purified product was obtained following preparative TLC (1 x 0.5 mm silica gel) using 6:4 EtOAc/hexanes as eluant. The purified product was characterized by <sup>1</sup>H  
5 NMR.

#### EXAMPLE 306

N-(2-Tetrahydrofuranylmethyl)-29,30,31,32-tetrahydro-nodulisporamide

To 40 mg N-(2-tetrahydrofuranylmethyl)-nodulisporamide in 2 mL  
10 methanol at room temperature was added 20 mg 10% Pd on carbon. One atmosphere of hydrogen was established and maintained for 2 hours using a balloon. After removal of the catalyst by filtration through Celite using methanol as eluant, the solution was concentrated under reduced pressure and 3 mg pure product was obtained following preparative TLC  
15 on silica gel (two 1000 micron plates). The product was characterized by NMR and mass spectrometry (m/z: 767 (M + 1)).

#### EXAMPLE 307

N-Ethyl-N-methyl-29,30,31,32-tetrahydro-nodulisporamide

20 To 23 mg of N-ethyl-N-methyl-nodulisporamide in 2 mL methanol at room temperature was added 40 mg 10% Pd on carbon. One atmosphere of hydrogen was established and maintained for 3 hours using a balloon. After removal of the catalyst by filtration through Celite  
25 using methanol as eluant, the solution was concentrated under reduced pressure and 9.5 mg of reduced product was obtained following medium pressure liquid chromatography (93/7 methanol/water as eluant). The product was characterized by proton NMR and mass spectrometry (m/z: 723 (M+1)).

30

#### EXAMPLE 308

General Procedure for the Preparation of  
29,30,31,32-Tetrahydro-nodulisporic Acid Derivatives

**EXAMPLE 311****General Procedure for the Preparation of  
29,30-Dihydro-Nodulisporic Acid Derivatives**

5

To a solution of 30 mg of 29,30-dihydro-nodulisporic acid in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of an amine or an alcohol selected from Table 6. Stir overnight at 4 °C and then at room temperature for 2 hours. Pour the solution into 1/1 saturated sodium bicarbonate/brine. Extract the solution with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution under reduced pressure. Pure product may be obtained following purification by flash chromatography, preparative TLC or reversed-phase liquid chromatography. Products may be characterized by proton NMR and or mass spectrometry.

15

**EXAMPLE 312****General Procedure for the Preparation of  
31,32-Dihydro-Compound B Derivatives**

20

Place 50 mg of a ester or amide analog prepared from compound B and the amines listed in Table 6 or alcohols listed in Table 2 in 4 mL methanol at room temperature. Hydrogenation of the 31,32-double bond may be accomplished using 10% Pd on carbon under 1 atmosphere of hydrogen from 15 minutes to 24 hours. The catalyst may be removed by filtration through a pad of Celite using methanol as eluant. Concentration of the solution under reduced pressure followed by purification on silica gel by either flash chromatography, preparative TLC or by reversed-phase liquid chromatography will yield the desired 31,32-dihydro-Compound B derivative.

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**nodulisporic acid**

Heat 20 mg of 29,30-dihydro-20,30-oxa-nodulisporyl azide in 8 mL toluene to 90 °C for 2 h. The solvent may be removed by  
5 evaporation and the product which is obtained may be characterized by proton NMR and mass spectrometry.

**EXAMPLE 316****32-Descarboxy-32-isocyanato-nodulisporic acid**

10

A solution of 54 mg of nodulisporyl azide in toluene was heated at 90°C for 2 h. The solvent was then evaporated and the isocyanate product was obtained in quantitative yield and was characterized by <sup>1</sup>H NMR and mass spectrometry.

15

**EXAMPLE 317****32-Descarboxy-32-(1-carbomethoxyamino)-nodulisporic acid**

To 1.3 mg of isocyanate of Example 313 in 1 mL of  
20 methanol was added 20 microliters of triethylamine. The reaction mixture was heated for 45 min at 75°C and the carbamate product (0.7 mg) was isolated by preparative TLC on silica gel (1 x 0.5 mm) and characterized by <sup>1</sup>H NMR and mass spectrometry.

25

**EXAMPLE 318****32-Descarboxy-32-(1-(3-benzyl)urea)-nodulisporic acid**

To 1 mg of isocyanate of Example 313 in 0.2 mL of toluene was added 40 microliters of benzylamine. The mixture was stirred at  
30 20°C for 20 min and the urea product (0.2 mg) was isolated by preparative TLC (1 x 0.5 mm silica gel, 1:3 hexane:EtOAc) and characterized by its <sup>1</sup>H NMR and MS.



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the isocyanate product thus obtained may be characterized by  $^1\text{H}$  NMR and mass spectrometry.

#### EXAMPLE 339

5                   General Procedure for the Synthesis of  
                  29,30-Dihydro-20,30-oxa-32-descarboxy-32-[UREA]- or  
                  29,30-Dihydro-20,30-oxa-32-descarboxy-32-[CARBAMATE]-  
                  Nodulisporic Acid Derivatives

10           To 1 mg of 29,30-dihydro-20,30-oxa-32-descarboxy-32-  
isocyanato-nodulisporic acid in 0.2 mL of toluene add 40 mg of an amine  
selected from Table 6 or alcohol selected from Table 2. Stir the mixture  
at 20°C from 20 minutes to 24 hours. Pure urea or carbamate product  
15 may be isolated by flash chromatography, preparative TLC or reversed-  
phase liquid chromatography. The purified products may be  
characterized by proton NMR and mass spectrometry.

#### EXAMPLE 340

20           31-Hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporyl azide

                  To 1 mg 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-  
nodulisporic acid in 0.2 mL chloroform add 0.05 mL triethylamine  
followed by 0.02 mL diphenylphosphoryl azide. Stir the reaction at room  
temperature for 3 h before purification by flash chromatography or  
25 preparative TLC on silica gel. The product which is obtained may be  
characterized by proton NMR and mass spectrometry.

#### EXAMPLE 341

30           31-Hydroxy-20,30-oxa-29,30,31,32-tetrahydro-32-descarboxy-32-  
isocyanato-nodulisporic acid

                  Heat a solution of 54 mg of 31-hydroxy-20,30-oxa-  
29,30,31,32-tetrahydro-nodulisporyl azide in toluene at 90°C for 2 h.

was purified by reversed-phase HPLC without workup using 30:70 to 15:85 (25 minute linear gradient) water/methanol to yield pure product. The product was characterized by  $^1\text{H}$  NMR.

5

**EXAMPLE 345****N-Ethyl-N-methyl-1-hydroxy-nodulisporamide**

To 30 mg N-ethyl-N-methyl-nodulisporamide in 2 mL tetrahydrofuran at room temperature was added 1 mL  
10 diisobutylaluminum hydride (1.0 M solution in hexanes). After 3 days at room temperature, the reaction was quenched by the addition of acetic acid. The solution was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated to dryness. The residue  
15 was purified by flash chromatography on silica gel using 1/1 acetone/hexanes as eluant. The purified product was characterized by proton NMR and mass spectrometry ( $m/z$ : 723 ( $M+1$ )).

**EXAMPLE 346****1-Hydroxy-Compound B or C**

20

To 5 mg of Compound B or C in 2 mL of methanol at  $0^\circ\text{C}$  under argon add 5 mg of sodium borohydride. After 10 min at  $0^\circ\text{C}$ , extract the products with methylene chloride. Dry the combined extracts over sodium sulfate and concentrate the solution in vacuo. The residual  
25 solid may be purified by flash chromatography, preparative TLC or reversed-phase liquid chromatography to yield 1-hydroxy-Compound B or C as a mixture of stereoisomers which may be characterized by proton NMR and mass spectrometry.

30

**EXAMPLE 347****General Procedure for Synthesis of 1-Hydroxy-Amide and Ester Derivatives of Compounds A, B and C**

## EXAMPLE 350

## 1-Hydroxy-1-Alkyl- or 1-Hydroxy-1-Aryl-Compounds A, B or C

- To 0.5 mL solution of 1.0 M Grignard reagent selected from Table
- 5 8 in 1/1 THF/toluene at 0°C add 1 mg Compound A, B or C dissolved in 0.6 mL THF. After 10 min at 0°C, quench the reaction with 2N HCl and extract with methylene chloride. Dry the combined organic layers over sodium sulfate, filter and concentrate under reduced pressure. Pure product may be obtained following flash chromatography, preparative
- 10 TLC or reversed-phase liquid chromatography. Purified products may be characterized by proton NMR or mass spectrometry.

## Table 8: Grignard Reagents

- 15 Methyl magnesium bromide  
Ethyl magnesium chloride  
iso-Propyl magnesium bromide  
Phenyl magnesium iodide  
Benzyl magnesium bromide
- 20 Allyl magnesium bromide  
Propargyl magnesium bromide  
Magnesium bromide acetylde

## EXAMPLE 351

- 25 1-Hydroxy-32-descarboxy-32-hydroxymethyl-nodulisporic acid

- To 1.2 mg methyl nodulisporate in 1.2 mL tetrahydrofuran at -78°C was added 20 µL 1M lithium aluminum hydride in tetrahydrofuran. The yellow color rapidly disappeared. After 10
- 30 minutes, the reaction was quenched at -78°C by dropwise addition of saturated Na<sub>2</sub>SO<sub>4</sub>. The solution was extracted with ethyl acetate, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Pure product was obtained following preparative TLC (1 x 0.25 mm silica gel

## EXAMPLE 354

## 4,20-bis-O-Acetyl-nodulisporic acid

5           To 1.2 mg of nodulisporic acid was added 300 microliters of acetic anhydride and 100 microliters of pyridine. The reaction mixture was heated at 65°C for 1 h and excess solvent was removed in vacuo. The residual solid was purified by preparative TLC on silica gel eluted with 95:5 dichloromethane:methanol to yield 1.2 mg of the bis-acetate  
10       characterized by its <sup>1</sup>H NMR.

## EXAMPLE 355

## N-Ethyl-N-methyl-20-dimethylaminocarbonyloxy-nodulisporamide

15           To 30 mg N-ethyl-N-methyl-nodulisporamide in 3 mL methylene chloride at 4 °C was added 60 mg carbonyldiimidazole. After 3 days at 4 °C, 1 mL dimethylamine (25% in water) was added and the solution stirred for an additional 4 days. The solution was poured into brine, extracted with methylene chloride, dried with sodium sulfate and  
20       evaporated to dryness. Product was partially purified by flash chromatography on silica gel using 4/6 acetone/hexanes as eluant. Additional purification using medium pressure liquid chromatography (92/8 methanol/water as eluant) yielded 18 mg pure product. The purified product was characterized by proton NMR and mass  
25       spectrometry (m/z: 792 (M+1)).

## EXAMPLE 356

## N-Ethyl-N-methyl-1-desoxo-1-methoximino-nodulisporamide

30           To a solution of 30 mg N-ethyl-N-methyl-nodulisporamide and 30 mg methoxylamine hydrochloride in 4 mL ethanol was added 0.1 mL pyridine. The solution was heated to reflux for 2 days, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with methylene chloride, washed with brine, dried over sodium

Similarly, amide and ester derivatives of compounds A, B and C, prepared using the amines listed in Table 6 and alcohols in Table 2, may be substituted for compounds A, B and C in the above procedure.

5    Table 9: Oxime Reagents

- Hydroxylamine
- O-Methylhydroxylamine
- O-Ethylhydroxylamine
- 10    O-Benzylhydroxylamine
- O-tert-Butylhydroxylamine
- O-(Pentafluorobenzyl)hydroxylamine
- O-Allylhydroxylamine
- O-Phenylhydroxylamine
- 15    O-iso-Butylhydroxylamine
- O-(2-Chloro-6-fluoro-benzyl)hydroxylamine
- O-(4-Methoxybenzyl)hydroxylamine

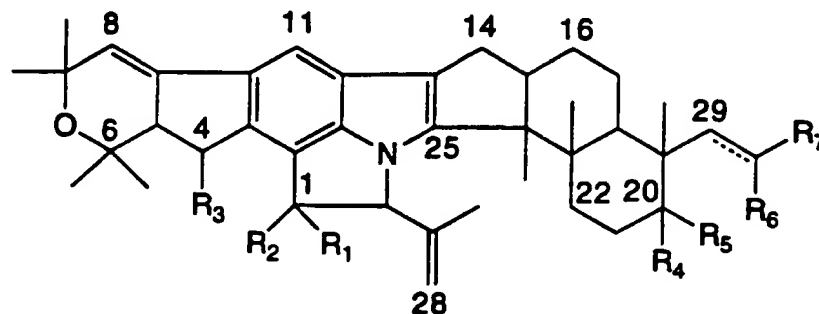
EXAMPLE 359

20    General Procedure for the Preparation of Hydrazinyl Derivatives of  
Compounds A, B and C

- To a solution of 20 mg of compound A, B or C and 20 mg hydrazine selected from Table 10 in 2 mL ethanol at room temperature,
- 25    add 0.02 mL pyridine. Heat the solution to reflux for 15 minutes to 24 hours, then cool to room temperature and dilute with methylene chloride. The solution may be washed with brine, the organic layer dried over sodium sulfate and concentrated to under reduced pressure. Pure product may be obtained following purification by flash chromatography or
- 30    preparative TLC on silica gel or reversed-phase liquid chromatography as a mixture of E- and Z-oxime isomers. The purified products may be characterized by proton NMR and mass spectrometry. Similarly, amide and ester derivatives of compounds A, B and C, prepared using the

WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

wherein

R<sub>1</sub> is

- (1) hydrogen,
- (2) optionally substituted C<sub>1</sub>-C<sub>10</sub> alkyl,
- (3) optionally substituted C<sub>2</sub>-C<sub>10</sub> alkenyl,
- (4) optionally substituted C<sub>2</sub>-C<sub>10</sub> alkynyl,
- (5) optionally substituted C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
- (6) optionally substituted C<sub>5</sub>-C<sub>8</sub> cycloalkenyl

where the substituents on the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are 1 to 3 groups independently selected from

- (i) C<sub>1</sub>-C<sub>5</sub> alkyl,
- (ii) X-C<sub>1</sub>-C<sub>10</sub> alkyl, where X is O or S(O)<sub>m</sub>.
- (iii) C<sub>3</sub>-C<sub>8</sub> cycloalkyl,
- (iv) hydroxy,
- (v) halogen,
- (vi) cyano,
- (vii) carboxy,
- (viii) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently hydrogen or C<sub>1</sub>-C<sub>10</sub> alkyl,
- (ix) C<sub>1</sub>-C<sub>10</sub> alkanoylamino, and

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- (8)  $\text{CH}_2\text{OCO}_2\text{R}^b$ ,
- (9)  $\text{CH}_2\text{OC}(\text{O})\text{NR}^c\text{R}^d$ ,
- (10)  $\text{C}(\text{O})\text{NR}^c\text{NR}^c\text{R}^d$ , or
- (11)  $\text{C}(\text{O})\text{NR}^c\text{SO}_2\text{R}^b$ ;

5      $\text{---}$  represents a single or a double bond;

$\text{R}^a$  is

- (1) hydrogen,
- (2) optionally substituted  $\text{C}_1\text{-C}_{10}$  alkyl,
- (3) optionally substituted  $\text{C}_3\text{-C}_{10}$  alkenyl,
- (4) optionally substituted  $\text{C}_3\text{-C}_{10}$  alkynyl,
- 10 (5) optionally substituted  $\text{C}_1\text{-C}_{10}$  alkanoyl,
- (6) optionally substituted  $\text{C}_3\text{-C}_{10}$  alkenoyl,
- (7) optionally substituted  $\text{C}_3\text{-C}_{10}$  alkynoyl,
- (8) optionally substituted aroyl,
- (9) optionally substituted aryl,
- 15 (10) optionally substituted  $\text{C}_3\text{-C}_7$  cycloalkanoyl,
- (11) optionally substituted  $\text{C}_5\text{-C}_7$  cycloalkenoyl,
- (12) optionally substituted  $\text{C}_1\text{-C}_{10}$  alkylsulfonyl
- (13) optionally substituted  $\text{C}_3\text{-C}_8$  cycloalkyl
- (14) optionally substituted  $\text{C}_5\text{-C}_8$  cycloalkenyl
- 20 where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl, cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl are from 1 to 10 groups independently selected from hydroxy,  $\text{C}_1\text{-C}_6$  alkoxy,  $\text{C}_3\text{-C}_7$  cycloalkyl, aryl  $\text{C}_1\text{-C}_3$  alkoxy,  $\text{NR}^e\text{R}^h$ ,  $\text{CO}_2\text{R}^b$ ,  $\text{CONR}^c\text{R}^d$  and halogen,
- 25 (15)  $\text{C}_1\text{-C}_5$  perfluoroalkyl,
- (16) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from  $\text{C}_1\text{-C}_5$  alkyl,  $\text{C}_1\text{-C}_5$  perfluoroalkyl, nitro, halogen and cyano,
- 30 (17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from  $\text{C}_1\text{-C}_5$  alkyl,  $\text{C}_1\text{-C}_5$  alkenyl,  $\text{C}_1\text{-C}_5$

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- (xix) formyl,  
 (xx) -NR<sub>g</sub>R<sup>h</sup>,  
 (xxi) 5 to 9-membered heterocycle, which may  
 be saturated or partially unsaturated, containing from 1 to 4  
 heteroatoms independently selected from oxygen, sulfur and  
 nitrogen, and optionally substituted with 1 to 5 groups  
 independently selected from R<sup>e</sup>,  
 (xxii) optionally substituted aryl, wherein the  
 aryl substituents are 1,2-methylenedioxy or 1 to 5 groups  
 independently selected from R<sup>e</sup>,  
 (xxiii) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy,  
 wherein the aryl substituents are 1,2-methylenedioxy or 1 to  
 5 groups independently selected from R<sup>e</sup>, and  
 (xxiv) C<sub>1</sub>-C<sub>5</sub> perfluoroalkyl;
- 15 R<sup>c</sup> and R<sup>d</sup> are independently selected from R<sup>b</sup>; or  
 R<sup>c</sup> and R<sup>d</sup> together with the N to which they are attached form a 3- to 10-  
 membered ring containing 0 to 2 additional heteroatoms  
 selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1  
 to 3 groups independently selected from R<sub>g</sub>, hydroxy, thioxo  
 and oxo;
- 20 R<sup>e</sup> is
- (1) halogen,
  - (2) C<sub>1</sub>-C<sub>7</sub> alkyl,
  - (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (4) -S(O)<sub>m</sub>R<sup>i</sup>,
  - (5) cyano,
  - (6) nitro,
  - (7) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,
  - (8) R<sup>i</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>v</sub>-,
  - (9) R<sup>i</sup>OCO(CH<sub>2</sub>)<sub>v</sub>,
  - (10) optionally substituted aryl where the substituents  
 are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, or  
 hydroxy,
  - (11) SO<sub>2</sub>NR<sub>g</sub>R<sup>h</sup>, or
  - (12) amino;



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- (4) optionally substituted aryl C<sub>0</sub>-C<sub>6</sub> alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and hydroxy;
- 5    m is        0 to 2; and  
      v is        0 to 3; or  
      a pharmaceutically acceptable salt thereof; and  
      excluding nodulisporic acid, 29,30-dihydro-20,30-oxa-nodulisporic acid,  
      and 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-  
 10       nodulisporic acid.

2.        A compound of Claim 1
- wherein  
      R<sub>1</sub> is
- 15        (1)        hydrogen,  
              (2)        optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
              (3)        optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl,  
              (4)        optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl,  
              (5)        optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl,  
              (6)        optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl
- 20        where the substituents on the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are 1 to 3 groups independently selected from
- (i)        C<sub>1</sub>-C<sub>3</sub> alkyl,  
              (ii)        X-C<sub>1</sub>-C<sub>6</sub> alkyl, where X is O or S(O)<sub>m</sub>,  
 25        (iii)        C<sub>5</sub>-C<sub>6</sub> cycloalkyl,  
              (iv)        hydroxy,  
              (v)        halogen,  
              (vi)        cyano,  
              (vii)        carboxy, and  
 30        (viii)        NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl,
- (7)        aryl C<sub>0</sub>-C<sub>3</sub> alkyl wherein said aryl is optionally substituted with 1 to 3 groups independently selected from R<sup>f</sup>,

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- (14) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl  
 where the substituents on the alkyl, alkenyl, alkynyl,  
 alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl,  
 cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl  
 5 are from 1 to 10 groups independently selected from  
 hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>5</sub>-C<sub>6</sub> cycloalkyl, aryl C<sub>1</sub>-C<sub>3</sub>  
 alkoxy, NR<sup>g</sup>R<sup>h</sup>, CO<sub>2</sub>R<sup>b</sup>, CONR<sup>c</sup>R<sup>d</sup> and halogen,
- (15) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (16) arylsulfonyl optionally substituted with 1 to 3  
 10 groups independently selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub>  
 perfluoroalkyl, halogen and cyano,
- (17) a 5- or 6-membered heterocycle containing 1 to 4  
 heteroatoms selected from oxygen, sulfur and nitrogen  
 optionally substituted by 1 to 4 groups independently  
 15 selected from C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkenyl, C<sub>1</sub>-C<sub>3</sub>  
 perfluoroalkyl, amino, C(O)NR<sup>c</sup>R<sup>d</sup>, cyano, CO<sub>2</sub>R<sup>b</sup> and  
 halogen, and which may be saturated or partly unsaturated;
- R<sup>b</sup> is
- (1) hydrogen,
- (2) optionally substituted aryl,
- (3) optionally substituted C<sub>1</sub>-C<sub>7</sub> alkyl,
- (4) optionally substituted C<sub>3</sub>-C<sub>7</sub> alkenyl,
- (5) optionally substituted C<sub>3</sub>-C<sub>7</sub> alkynyl,
- (6) optionally substituted C<sub>5</sub>-C<sub>7</sub> cycloalkyl,
- (7) optionally substituted C<sub>5</sub>-C<sub>7</sub> cycloalkenyl, or
- (8) optionally substituted 5- to 10-membered  
 25 heterocycle containing from 1 to 4 heteroatoms  
 independently selected from oxygen, sulfur and nitrogen;  
 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
 cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
 30 independently selected from
- (i) hydroxy,
- (ii) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (iii) oxo,
- (iv) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>,

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- (8)  $R^iCO_2(CH_2)_v-$ ,  
 (9)  $R^iOCO(CH_2)_v$ ,  
 (10) optionally substituted aryl where the substituents  
 are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, or  
 hydroxy, or  
 (11)  $SO_2NR^gR^h$ ;  
 5  $R^f$  is  
 (1) methyl,  
 (2) X-C<sub>1</sub>-C<sub>2</sub> alkyl, where X is O or S(O)<sub>m</sub>,  
 (3) halogen,  
 10 (4) acetylamino,  
 (5) trifluoromethyl,  
 (6)  $NY^1Y^2$ , where Y<sup>1</sup> and Y<sup>2</sup> are independently H or  
 methyl, and  
 (7) hydroxy;  
 15  $R^g$  and  $R^h$  are independently  
 (1) hydrogen,  
 (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy ,  
 amino, or CO<sub>2</sub>R<sup>i</sup>  
 (3) aryl optionally substituted with halogen, 1,2-  
 20 methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub>  
 perfluoroalkyl,  
 (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally  
 substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy;  
 (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 25 (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,  
 (7) C<sub>1</sub>-C<sub>5</sub> alkanoyl C<sub>1</sub>-C<sub>6</sub> alkyl,  
 (9) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,  
 (10) aminocarbonyl,  
 (11) C<sub>1</sub>-C<sub>5</sub> monoalkylaminocarbonyl  
 30 (12) C<sub>1</sub>-C<sub>5</sub> dialkylaminocarbonyl; or  
 $R^g$  and  $R^h$  together with the N to which they are attached form a 5- to 6-  
 membered ring containing 0 to 2 additional heteroatoms  
 selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1  
 to 3 groups independently selected from R<sup>e</sup> and oxo;

- (6)  $\text{CH}_2\text{OR}^{\text{a}}$ ,  
 (7)  $\text{CH}_2\text{OCO}_2\text{R}^{\text{b}}$ ,  
 (8)  $\text{CH}_2\text{OC}(\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ,  
 (9)  $\text{C}(\text{O})\text{NR}^{\text{c}}\text{NR}^{\text{c}}\text{R}^{\text{d}}$ , or  
 (10)  $\text{C}(\text{O})\text{NR}^{\text{c}}\text{SO}_2\text{R}^{\text{b}}$ ;  
 5  $\text{R}^{\text{a}}$  is  
 (1) hydrogen,  
 (2) optionally substituted  $\text{C}_1\text{-C}_4$  alkyl,  
 (3) optionally substituted  $\text{C}_3\text{-C}_4$  alkenyl,  
 (4) optionally substituted  $\text{C}_3\text{-C}_4$  alkynyl,  
 10 (5) optionally substituted  $\text{C}_1\text{-C}_4$  alkanoyl,  
 (6) optionally substituted aroyl,  
 (7) optionally substituted  $\text{C}_5\text{-C}_6$  cycloalkanoyl,  
 (8) optionally substituted  $\text{C}_5\text{-C}_6$  cycloalkenoyl,  
 (9) optionally substituted  $\text{C}_1\text{-C}_3$  alkylsulfonyl  
 15 where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, aroyl, cycloalkanoyl, cycloalkenoyl, and alkylsulfonyl, are from 1 to 5 groups independently selected from hydroxy,  $\text{C}_1\text{-C}_2$  alkoxy, aryl  $\text{C}_1\text{-C}_3$  alkoxy,  $\text{NR}^{\text{g}}\text{R}^{\text{h}}$ ,  $\text{CO}_2\text{R}^{\text{b}}$ ,  $\text{CONR}^{\text{c}}\text{R}^{\text{d}}$  and halogen,  
 20 (10) trifluoromethyl,  
 (11) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from methyl, trifluoromethyl and halogen,  
 (12) a 5- or 6-membered heterocycle containing 1 to 4  
 25 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from methyl, trifluoromethyl,  $\text{C}(\text{O})\text{NR}^{\text{c}}\text{R}^{\text{d}}$ ,  $\text{CO}_2\text{R}^{\text{b}}$  and halogen, and which may be saturated or partly unsaturated;  
 30  $\text{R}^{\text{b}}$  is  
 (1) hydrogen,  
 (2) optionally substituted aryl,  
 (3) optionally substituted  $\text{C}_1\text{-C}_6$  alkyl,  
 (4) optionally substituted  $\text{C}_3\text{-C}_6$  alkenyl,  
 (5) optionally substituted  $\text{C}_3\text{-C}_6$  alkynyl,

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(xx) optionally substituted aryl, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from  $R^e$ ,

(xxi) optionally substituted aryl C<sub>1</sub>-C<sub>3</sub> alkoxy, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from  $R^e$ , and

(xxii) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl;

$R^e$  is

- (1) halogen,
- (2) C<sub>1</sub>-C<sub>3</sub> alkyl,
- (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
- (4) -S(O)<sub>m</sub>R<sup>i</sup>,
- (5) cyano,
- (6) R<sup>i</sup>O(CH<sub>2</sub>)<sub>v</sub>-,
- (7) R<sup>i</sup>CO<sub>2</sub>(CH<sub>2</sub>)<sub>v</sub>-,
- (8) R<sup>i</sup>OCO(CH<sub>2</sub>)<sub>v</sub>,
- (9) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C<sub>1</sub>-C<sub>3</sub> alkyl, C<sub>1</sub>-C<sub>3</sub> alkoxy, or hydroxy,

(10) SO<sub>2</sub>NR<sup>g</sup>R<sup>h</sup>, or

(11) amino;

$R^f$  is

- (1) methyl,
- (2) X-C<sub>1</sub>-C<sub>2</sub> alkyl, where X is O or S(O)<sub>m</sub>,
- (3) trifluoromethyl,
- (4) NY<sup>1</sup>Y<sup>2</sup>, where Y<sup>1</sup> and Y<sup>2</sup> are independently H or methyl,
- (5) hydroxy,
- (6) halogen, and
- (7) acetylamino,

R<sup>g</sup> and R<sup>h</sup> are independently

- (1) hydrogen,
- (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or CO<sub>2</sub>R<sup>i</sup>

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- (2)  $C(O)N(OR^b)R^c$ ,
- (3)  $C(O)NR^cR^d$ ,
- (4)  $C(O)NR^cNR^cR^d$ , or
- (5)  $C(O)NR^cSO_2R^b$

5  $R^8, R^9, R^b, R^c$  and  $R^d$  are as defined in Claim 1.

6. A compound of Claim 5 wherein  
 $R_{10}$  is  $C(O)OR^b$ ;

$R^b$  is

10

- (1) optionally substituted aryl,
  - (2) optionally substituted  $C_1$ - $C_6$  alkyl,
  - (3) optionally substituted  $C_3$ - $C_6$  alkenyl,
  - (4) optionally substituted  $C_3$ - $C_6$  alkynyl,
  - (5) optionally substituted  $C_3$ - $C_6$  cycloalkyl, or
  - (6) optionally substituted 5 to 6-membered heterocycle
- 15 containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;  
 where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from

20

- (i) hydroxy,
- (ii)  $C_1$ - $C_3$  alkyl,
- (iii) oxo,
- (iv)  $SO_2NR^gR^h$ ,
- (v) aryl  $C_1$ - $C_3$  alkoxy,
- 25 (vi) hydroxy  $C_1$ - $C_4$  alkyl,
- (vii)  $C_1$ - $C_4$  alkoxy,
- (viii) hydroxy  $C_1$ - $C_4$  alkoxy,
- (ix) amino  $C_1$ - $C_4$  alkoxy,
- (x) cyano,
- 30 (xi)  $C_1$ - $C_4$  alkyl-S(O) $m$ ,
- (xii)  $C_5$ - $C_6$  cycloalkyl optionally substituted with 1 to 4 groups independently selected from  $R^c$ ,
- (xiii)  $C_5$ - $C_6$  cycloalkenyl,
- (xiv) halogen,

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selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from R<sup>e</sup> and oxo;

R<sup>i</sup> is (1) hydrogen, or  
(2) C<sub>1</sub>-C<sub>6</sub> alkyl;

5 m is 0 to 2; and

all other variables are as defined in Claim 5.

7. A compound of Claim 5 wherein  
10 R<sup>10</sup> is (1) C(O)N(OR<sup>b</sup>)R<sup>c</sup>,  
(2) C(O)NR<sup>c</sup>R<sup>d</sup>  
(3) C(O)NR<sup>c</sup>NR<sup>c</sup>R<sup>d</sup>, or  
(4) C(O)NR<sup>c</sup>SO<sub>2</sub>R<sup>i</sup>;

R<sup>b</sup>, R<sup>c</sup>, R<sup>d</sup> and R<sup>i</sup> are as defined in Claim 5.

15 8. A compound of Claim 3 wherein  
R<sup>10</sup> is C(O)NR<sup>c</sup>R<sup>d</sup>; and  
R<sup>c</sup> and R<sup>d</sup> are as defined in Claim 3.

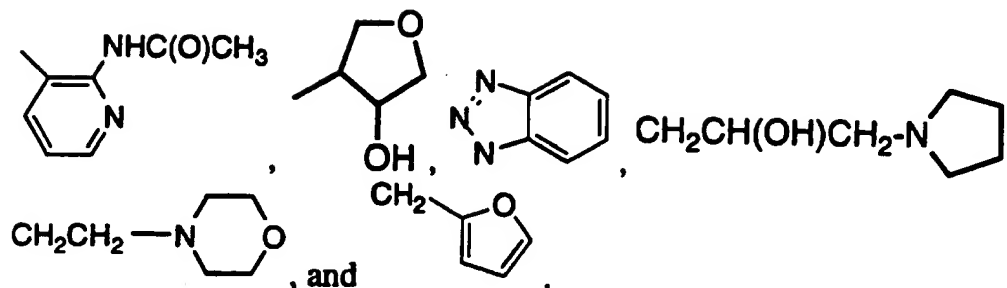
20 9. A compound of Claim 5 wherein  
R<sup>10</sup> is C(O)NR<sup>c</sup>R<sup>d</sup>;  
R<sup>b</sup> is (1) hydrogen,  
(2) optionally substituted aryl,  
(3) optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl,  
(4) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkenyl,  
25 (5) optionally substituted C<sub>3</sub>-C<sub>6</sub> alkynyl,  
(6) optionally substituted C<sub>3</sub>-C<sub>6</sub> cycloalkyl,  
(7) optionally substituted C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, or  
(8) optionally substituted 5 to 6-membered heterocycle  
30 containing from 1 to 4 heteroatoms independently selected  
from oxygen, sulfur and nitrogen;  
where the substituents on the aryl, alkyl, alkenyl, cycloalkyl,  
cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups  
independently selected from  
(i) hydroxy,

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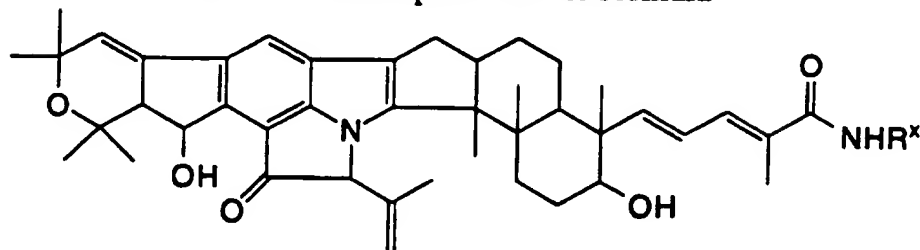
- $R^e$  is
- (1) halogen,
  - (2) C<sub>1</sub>-C<sub>3</sub> alkyl,
  - (3) C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (4)  $R^iO(CH_2)_v$ ,
  - 5 (5)  $R^jCO_2(CH_2)_v$ ,
  - (6)  $R^iOCO(CH_2)_v$ ,
  - (7)  $SO_2NR^gR^h$ ;
  - (8) amino
- $v$  is 0;
- 10  $R^g$  and  $R^h$  are independently
- (1) hydrogen,
  - (2) C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with hydroxy, amino, or  $CO_2R^i$ ,
  - 15 (3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C<sub>1</sub>-C<sub>7</sub> alkoxy, C<sub>1</sub>-C<sub>7</sub> alkyl or C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl,
  - (4) aryl C<sub>1</sub>-C<sub>6</sub> alkyl, wherein the aryl is optionally substituted with C<sub>1</sub>-C<sub>3</sub> perfluoroalkyl or 1,2-methylenedioxy,
  - 20 (5) C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
  - (6) C<sub>1</sub>-C<sub>5</sub> alkanoyl,
  - (7) aryl C<sub>1</sub>-C<sub>5</sub> alkoxycarbonyl,
  - (8) aminocarbonyl, or
- 25  $R^g$  and  $R^h$  together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)<sub>m</sub>, and N, optionally substituted with 1 to 3 groups independently selected from  $R^e$  and oxo;
- $R^i$  is
- (1) hydrogen or
  - 30 (2) optionally substituted C<sub>0</sub>-C<sub>6</sub> alkyl wherein the substituents are aryl or substituted aryl, and the aryl substituents are from 1 to 3 groups independently selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, and hydroxy; and
- all other variables are as defined in Claim 5.



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13. A compound of the formula

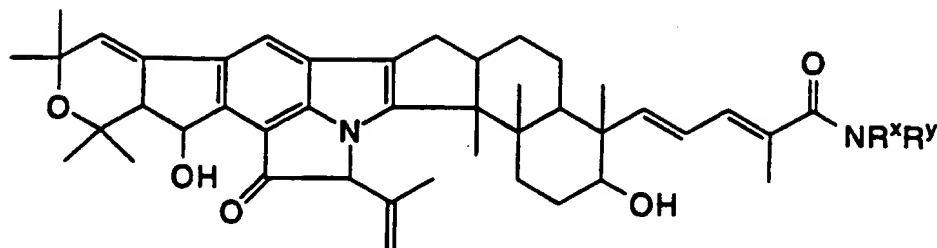


5

wherein  $\text{R}^X$  is selected from the group consisting of:

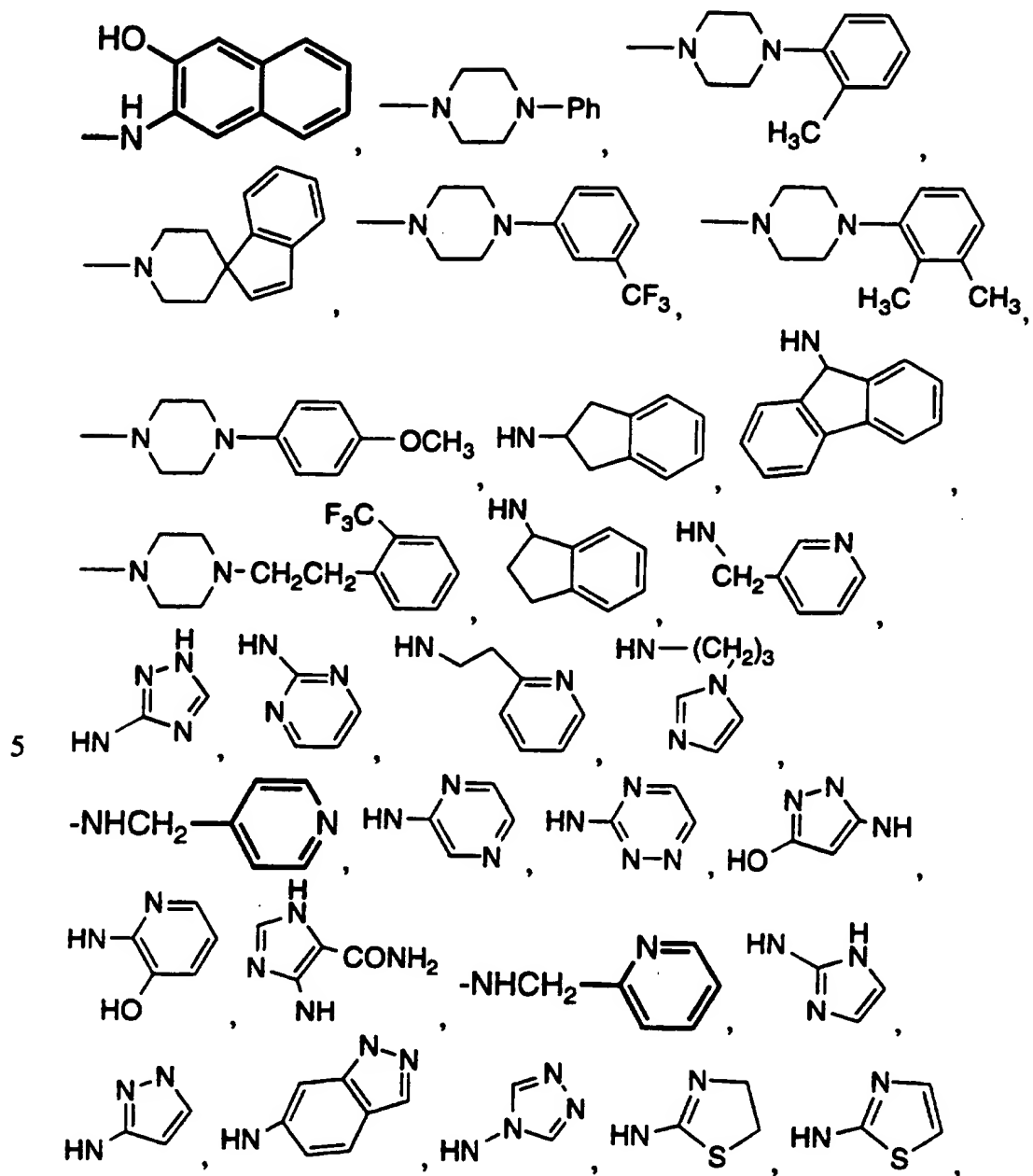
- H,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{C}(\text{CH}_3)_3$ ,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}_2\text{OH}$ ,  
 $\text{CH}(\text{CO}_2\text{CH}_3)\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{CO}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}(\text{OCH}_2\text{CH}_3)_2$ ,  
 $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ ,  $\text{CH}(\text{CH}_3)(\text{CH}_2)_3\text{C}(\text{CH}_3)_2\text{OH}$ ,  $(\text{CH}_2)_3\text{OH}$ ,  
 10  $(\text{CH}_2)_4\text{OH}$ ,  $(\text{CH}_2)_5\text{OH}$ ,  $\text{CH}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_3$ ,  $\text{NHC}(\text{CH}_3)_3$ ,  $\text{CH}_2\text{CN}$ ,  
 $(\text{CH}_2)_6\text{OH}$ ,  $\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_2\text{CH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{SCH}_3$ ,  $\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CONH}_2$ ,  
 $\text{CH}(\text{CH}_3)(\text{CH}_2\text{OH})_2$ ,  $\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{OH}$ ,  
 $\text{CH}(\text{CH}_2\text{OH})(\text{CH}_2)_3\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{OCH}_3)\text{CH}_3$ ,  $(\text{CH}_2)_2\text{SH}$ ,  
 15  $(\text{CH}_2)_4\text{NH}_2$ ,  $\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$ ,  
 $\text{CH}(\text{CH}(\text{CH}_3)_2)\text{CH}_2\text{OH}$ ,  $(\text{CH}_2)_3\text{NH}_2$ ,  $(\text{CH}_2)_3\text{N}(\text{CH}_2\text{CH}_3)_2$ ,  
 $(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$ ,  $\text{OCH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$ ,  $\text{OCH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $\text{CH}_2\text{CH}_2\text{NHC}(\text{O})\text{CH}_3$ ,  $\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$ ,  $c\text{-C}_3\text{H}_5$ ,  $c\text{-C}_6\text{H}_{11}$ ,  
 $(\text{CH}_2)_3\text{OCH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}=\text{CH}_2$ ,  $\text{C}(\text{CH}_2\text{CH}_3)(\text{CH}_2\text{OH})_2$ ,  
 20  $\text{CH}_2\text{C}\equiv\text{CH}$ ,  $\text{CH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}_2\text{CH}_2\text{F}$ ,  $(\text{CH}_2)_3\text{O}(\text{CH}_2)_{11}\text{CH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NH}_2$ ,  $\text{CH}_2\text{CF}_3$ ,  
 $\text{NHCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CH}_3)\text{CO}_2\text{CH}_3$ ,  $\text{C}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$ ,  
 $\text{CH}(\text{CO}_2\text{CH}_2\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)\text{CO}_2\text{CH}_3$ ,  
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $\text{C}(\text{CH}_3)_2\text{C}\equiv\text{CH}$ ,  $(\text{CH}_2)_4\text{CH}_3$ ,  $\text{CH}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$ .

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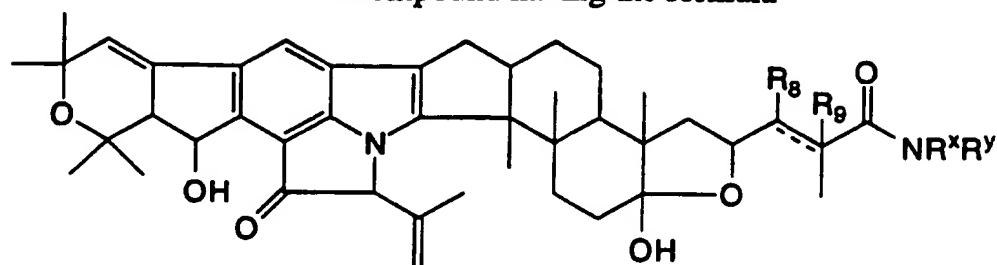
wherein  $\text{NR}^{\text{X}}\text{R}^{\text{Y}}$  is selected from the group consisting of:

- $\text{N}(\text{CH}_3)\text{CH}_2\text{C}\equiv\text{N}$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_3$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$ ,  
 $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  
 5  $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$ ,  
 $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{N}(\text{CH}_2\text{CH}=\text{CH}_2)_2$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$ ,  
 $\text{N}(\text{CH}_2\text{CH}(\text{CH}_3)\text{OH})_2$ ,  $\text{N}(\text{CH}_2\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$ ,  
 $\text{N}(\text{CH}_2\text{CH}_3)\text{CH}(\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$ ,  
 $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$ ,  
 10  $\text{N}((\text{CH}_2)_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$ ,  $\text{N}(\text{CH}_3)\text{CH}_2\text{C}\equiv\text{CH}$ ,  $\text{N}((\text{CH}_2)_8\text{CH}_3)_2$ ,  
 $\text{N}((\text{CH}_2)_7\text{CH}_3)_2$ ,  $\text{N}(\text{CH}_3)(\text{CH}_2)_2\text{NHCH}_3$ ,  $\text{N}(\text{CH}_3)(\text{CH}_2)_3\text{NH}_2$ ,  
 $\text{NHCH}(\text{CH}_2\text{OH})\text{CH}_2\text{Ph}$ ,  $\text{NHPh}(2\text{-OH}, 4\text{-CH}_3)$ ,  $\text{NHCH}_2\text{Ph}(4\text{-NH}_2)$ ,  
 $\text{NHPh}(4\text{-Cl})$ ,  $\text{NHPh}(4\text{-CH}_2\text{CH}_2\text{OH})$ ,  $\text{NHPh}(2\text{-CH}_2\text{CH}_2\text{OH})$ ,  
 $\text{NHCH}_2\text{CH}_2\text{Ph}$ ,  $\text{NHPh}(2\text{-CH}_2\text{OH})$ ,  $\text{NHPh}(3\text{-N}(\text{CH}_3)_2)$ ,  $\text{NHPh}(4\text{-SO}_2\text{NH}_2)$ ,  
 15  $\text{NHNHPh}$ ,  $\text{NHPh}(2\text{-CONH}_2)$ ,  $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-OH})$ ,  
 $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-SO}_2\text{NH}_2)$ ,  $\text{NHPh}(2\text{-NH}_2)$ ,  
 $\text{NHCH}(\text{CH}_2\text{CH}(\text{CH}_3)_2)\text{CO}_2\text{CH}_2\text{Ph}$ ,  $\text{NH}\text{SO}_2\text{CH}_2\text{Ph}(4\text{-C}(\text{CH}_3)_3)$ ,  
 $\text{NH}\text{SO}_2\text{CH}_2\text{Ph}$ ,  $\text{NHNHPh}(2\text{-F})$ ,  $\text{NHCH}_2\text{Ph}(4\text{-CF}_3)$ ,  $\text{NHPh}(4\text{-OCH}_2\text{Ph})$ ,  
 $\text{NHPh}(4\text{-SCH}_3)$ ,  $\text{NHCH}(\text{CH}_2\text{Ph})\text{CO}_2\text{CH}_2\text{CH}_3$ ,  
 20  $\text{NHCH}(\text{CH}_2\text{Ph})\text{CO}_2\text{CH}_3$ ,  $\text{NHCH}_2\text{Ph}(4\text{-OCH}_3)$ ,  $\text{NHCH}_2\text{-1-naphthyl}$ ,  
 $\text{NHPh}(4\text{-F})$ ,  $\text{NHCH}_2\text{Ph}(2\text{-F})$ ,  $\text{NHCH}_2\text{CH}(\text{Ph})\text{OH}$ ,  $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-F})$ ,  
 $\text{NHC}(\text{CH}_3)_2\text{CH}_2\text{Ph}(3\text{-F})$ ,  $\text{NHPh}(3,4\text{-diF})$ ,  $\text{NHCH}_2\text{Ph}(3\text{-CH}_3)$ ,  $\text{NHNH}(3\text{-CH}_3)\text{Ph}$ ,  
 $\text{NHCH}_2\text{Ph}(2\text{-Cl})$ ,  $\text{NHCH}_2\text{Ph}(2,4\text{-diCl})$ ,  $\text{NHNHPh}(4\text{-CH}_3)$ ,  
 $\text{NHCH}_2\text{Ph}(4\text{-Cl})$ ,  $\text{NH}(\text{CH}_2)_3\text{Ph}$ ,  $\text{NHCH}_2\text{CH}_2\text{Ph}(4\text{-Cl})$ ,  
 25  $\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{Ph}$ ,  $\text{NHCH}_2\text{Ph}(3\text{-CF}_3)$ ,  $\text{NHCH}_2\text{Ph}(2\text{-CF}_3)$ ,  
 $\text{NH}(\text{CH}_2)_4\text{Ph}$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,  
 $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,  $\text{N}(\text{CH}_2\text{Ph})(\text{CH}_2)_3\text{CH}_3$ ,  $\text{NH}\text{OCH}_2\text{Ph}$ ,  
 $\text{NCH}_2\text{Ph}(2,6\text{-diF})$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,  $\text{NHCH}(\text{CH}_3)\text{Ph}$ ,  
 $\text{N}(\text{CH}_3)\text{CH}_2\text{Ph}$ ,  $\text{NHCH}_2\text{Ph}(3,4\text{-diCl})$ ,  $\text{N}(\text{CH}_3)\text{CH}(\text{CH}_3)\text{Ph}$ ,



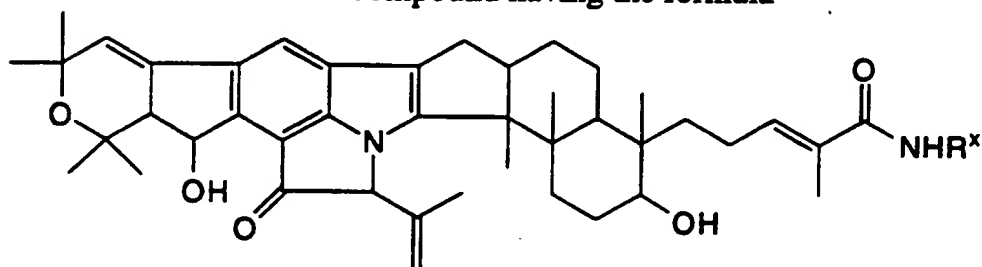
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17. A compound having the formula



- 5 wherein R<sub>8</sub> and R<sub>9</sub> are hydrogen and separated by a double bond or R<sub>8</sub> is hydroxy, R<sub>9</sub> is hydrogen and separated by a single bond and NR<sup>x</sup>R<sup>y</sup> is as defined in Claim 14.

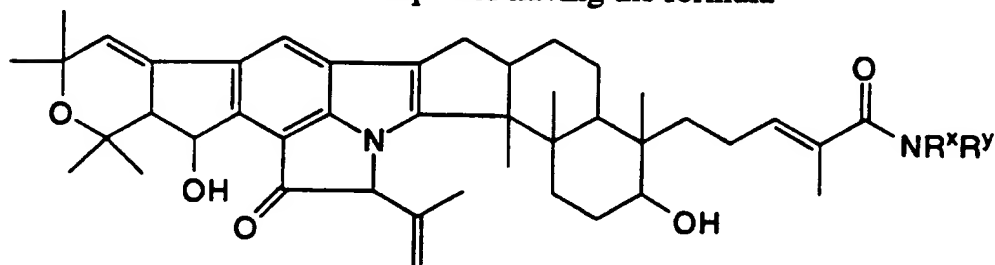
18. A compound having the formula



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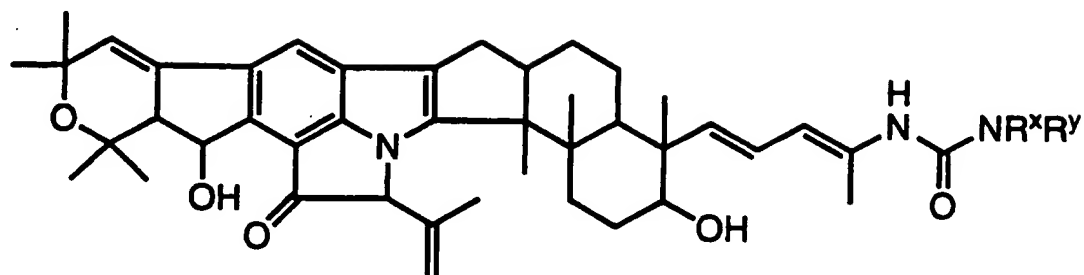
wherein R<sup>x</sup> is as defined in Claim 13.

19. A compound having the formula



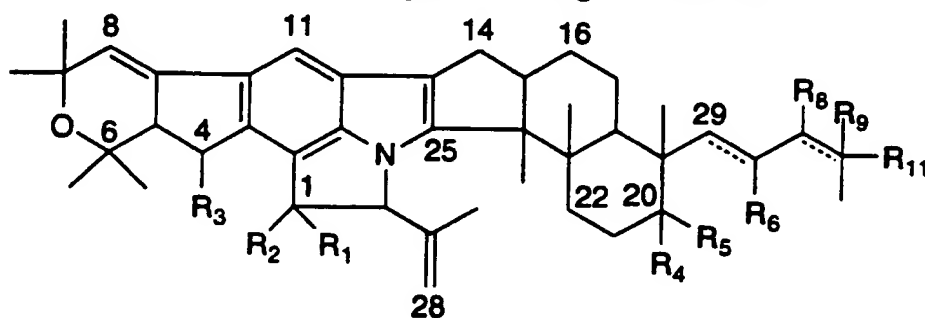
15

wherein NR<sup>x</sup>R<sup>y</sup> is as defined in Claim 14.



wherein  $\text{NR}^x\text{RY}$  is as defined in Claim 14.

5                    24.           A compound having the formula



where R<sub>1</sub> - R<sub>6</sub>, R<sub>8</sub> and R<sub>9</sub> are as defined in Claim 1;

**R<sub>11</sub> is**

(1)	COCl,
(2)	CON <sub>3</sub> , or
(3)	NCO.

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25. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

26. A composition of Claim 25 further comprising an anthelmintic agent.

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27. A composition of Claim 26 wherein said anthelmintic agent is selected from ivermectin, avermectin, abamectin, emamectin, eprinaectin, doramectin,

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/03611

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/40, 31/425, 31/445, 31/495; C07D 405/06, 487/16  
US CL : 514/233.2, 255, 322, 365, 397; 544/142, 310; 546/199; 548/417

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/233.2, 255, 322, 365, 397; 544/142, 310; 546/199; 548/417

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Structure

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,399,582 A (A. W. DOMBROWSKI ET AL.) 21 March 1995, columns 1-2, compounds 1-3.	1-3, 5-6, 11-12, 15, 25-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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* E		earlier document published on or after the international filing date
* L		document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
* O		document referring to an oral disclosure, use, exhibition or other means
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	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search

10 MAY 1996

Date of mailing of the international search report

20 MAY 1996

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